Paid Circulation, 35,829

The New England Journal of Medicine

FORMERLY THE BOSTON MEDICAL AND SURGICAL JOURNAL — *Established 1828*

VOLUME 253 AUGUST 18, 1955 NUMBER 7

Original Articles

The Utility of the Blood Pepsin Assay in Clinical Medicine 261
Howard M. Spiro, Anna E. Ryan and Chester M. Jones

Therapeutic Factors in Survival After Lethal Cholinesterase Inhibition by Phosphorus Insecticides 266
Gustave Freeman and Marvin A. Epstein

Congenital Cardiac Malformations in the Neonatal Period: An Autopsy Study . . . 271
William B. Ober and Thomas E. Moore, Jr.

Acute Disseminated Encephalomyelitis Treated with ACTH: Report of a Case 275
Ben Selling and Edward Meilman

Medical Progress

Cardiac Disease in Pregnancy 279
Julius Abramson and Benjamin Tenney

Massachusetts Medical Society 297
Civil Defense Agency 298
Notices 302

Medical Intelligence

Interference with Uptake of Radioiodine Tracer during the Administration of Vitamin-Mineral Mixtures 286
Lawrence A. Kohn and Edna B. Nichols

The British Medical Association in Toronto . 287
John W. P. Thompson

Case Records of the Massachusetts General Hospital . . 288

Editorials

The Canadian Meeting 296
Under the Big Top 296
Polio Panic 297

Correspondence 299
Books Received 300

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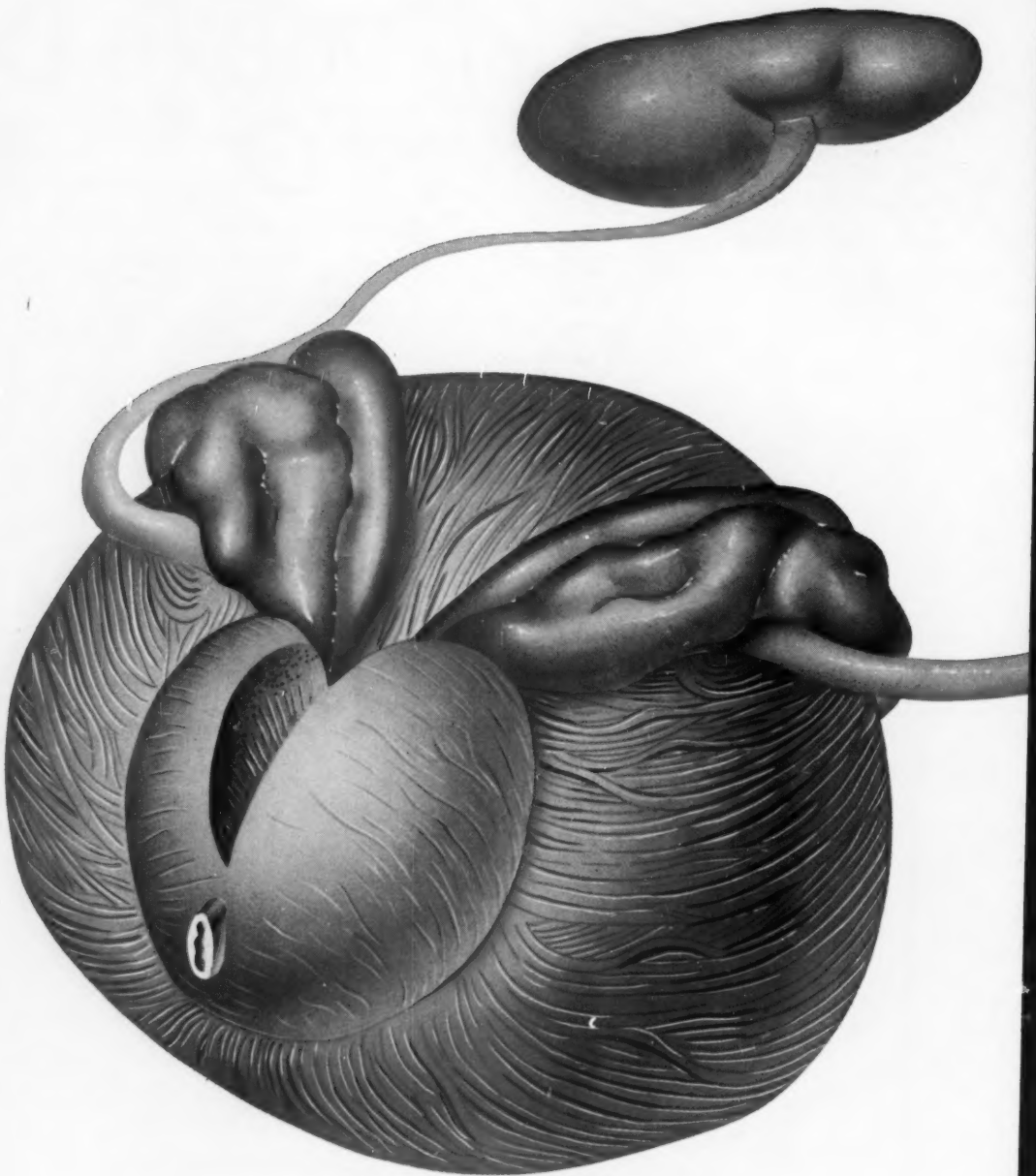

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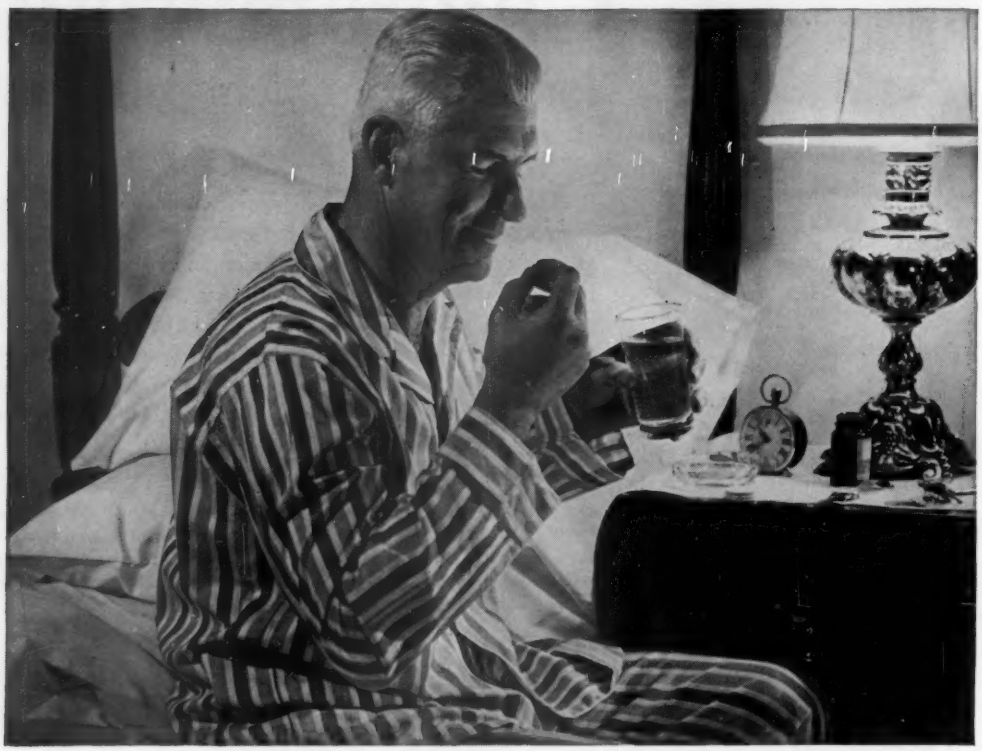

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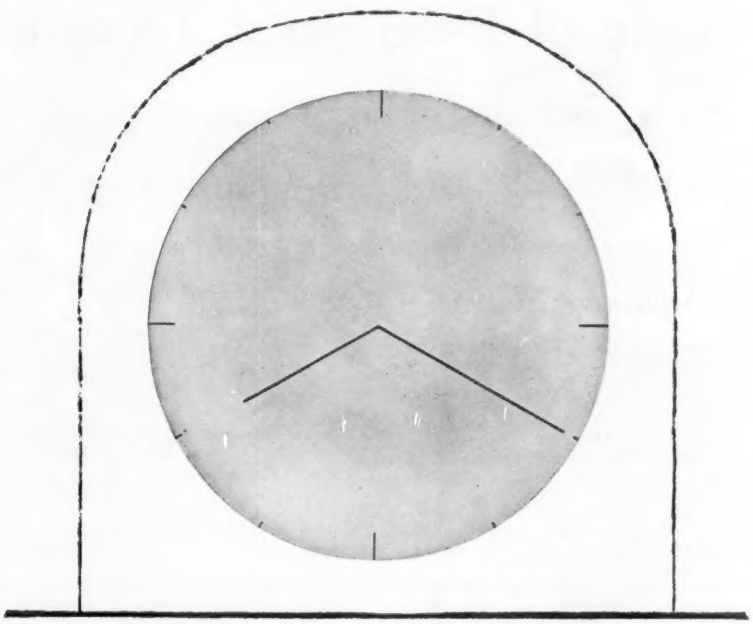
Entered as second-class matter, November 16, 1932, at the post office at Boston, Massachusetts, under the Act of March 3, 1879. Published weekly at 8 Fenway, Boston 15. Domestic, $8.00 per year.



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Thursday, September 29, 1955

9:00 Combined psychologic-physiologic treatment of Mental Disorder — Neurophysiologic Foundation.
Robert Arnot, M.D.
Boston

10:00 Clinical Demonstrations:
1. Electroshock, with special emphasis on relaxation by succinyl choline chloride (anectine).
2. Nonconvulsive treatment.
3. Combined convulsive - nonconvulsive treatment of 2 minutes' duration (shock-countershock technique).

Leo Alexander, M.D.
Irving E. Gilbert, M.D.
Boston

12:00 Summary and question period.
12:30 Group Discussion at lunch.
TOPIC: Experiences in treating schizophrenia.
Moderator: Robert Arnot, M.D.

Symposium and Group Discussion on New Drugs Including Thorazine and Reserpine

2:00 Clinical Physiology of Reserpine.
Robert W. Wilkins, M.D.
Boston

3:00 Clinical Physiology of Thorazine.
Dale G. Friend, M.D.
Boston

4:00 The Use of Thorazine and Reserpine in Psychiatric Practice.
Milton Greenblatt, M.D.
Walter Mann, M.D.
Boston

8:30 Meeting at Harvard Club.
Report of Discussion Groups.

Friday, September 30, 1955

9:00 Anxiety as a Symptom and as Etiology; The Concept of the Vicious Cycle.
Irving M. Rosen, M.D.
Boston

10:00 Clinical Demonstration:
Electronarcosis.
Esther Bogen Tietz, M.D.
Los Angeles

11:00 Treatment exercises by participants under supervision.
12:00 Summary and question period.
12:30 Group Discussion at lunch.
TOPIC: Experiences in treating Anxiety.
Moderator: Robert Arnot, M.D.

Symposium on Patient Management and Rehabilitation

2:00 Management of the Hospital Community.
Robert W. Hyde, M.D.
Boston

3:00 Rehabilitation — Early and Late.
Walter E. Barton, M.D.
Boston

4:00 Management of the Office Patient and his Family in Private Practice. Rehabilitation in Office Practice.
Merrill Moore, M.D.
Boston

7:00 Dinner, Harvard Club.
Report of Discussion Groups.

Saturday, October 1, 1955

9:00 Treatment of Mental Disorder — Rationale and Indications, Integration of Physical Treatment with Dynamic Psychotherapy.
Leo Alexander, M.D.

10:00 Clinical Demonstration:
Electric Coma.
Brian C. Campden-Main
Petersburg, Virginia

11:00 Treatment exercises by participants under supervision.
Leo Alexander, M.D.
Samuel E. White, M.D.
Boston

12:00 Summary and question period.
12:30 Luncheon.

Symposium and Group Discussion on Psychotherapy

2:00 Psychotherapy.
Hans Lowenbach, M.D.
Durham, North Carolina

3:00 Analytic Psychotherapy of the Psychoses.
John N. Rosen, M.D.
New York

4:00 Group Discussion and Summary.

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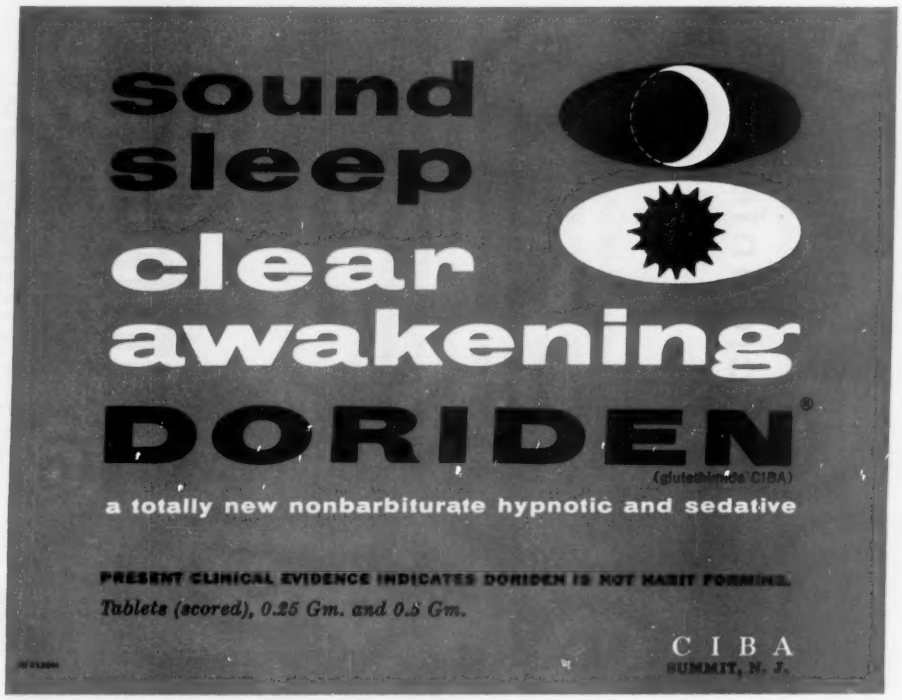

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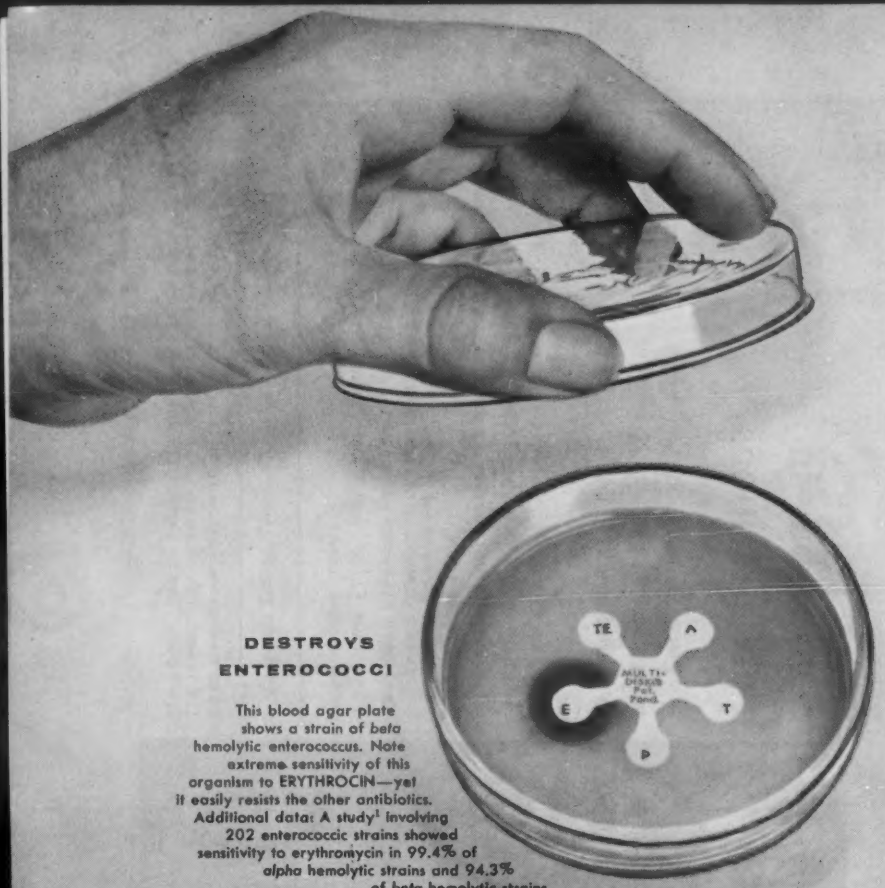

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1. Eisenberg, et al., Antib. & Chemo., 3:1026-1028, Oct., 1953.

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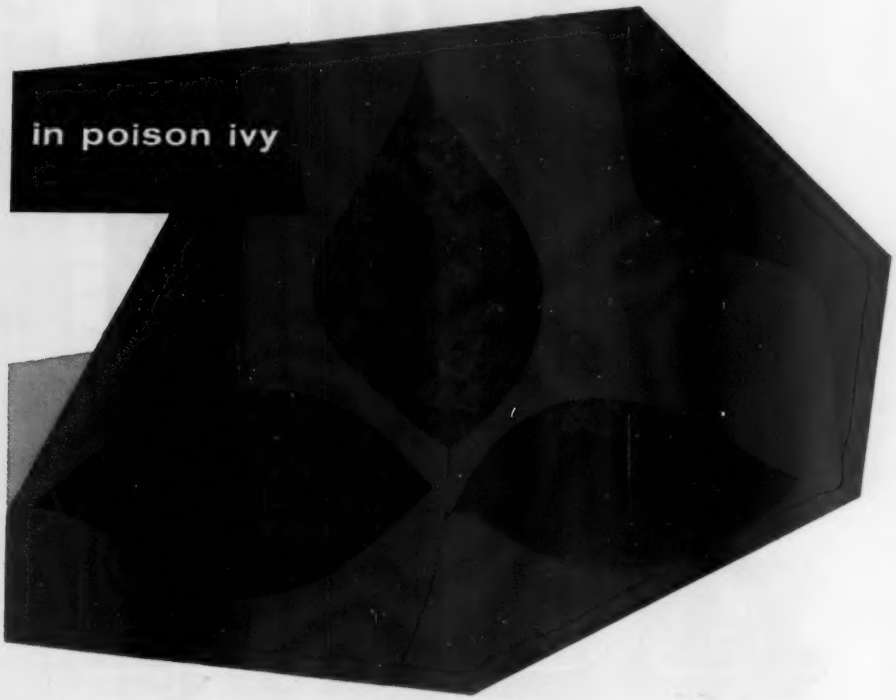

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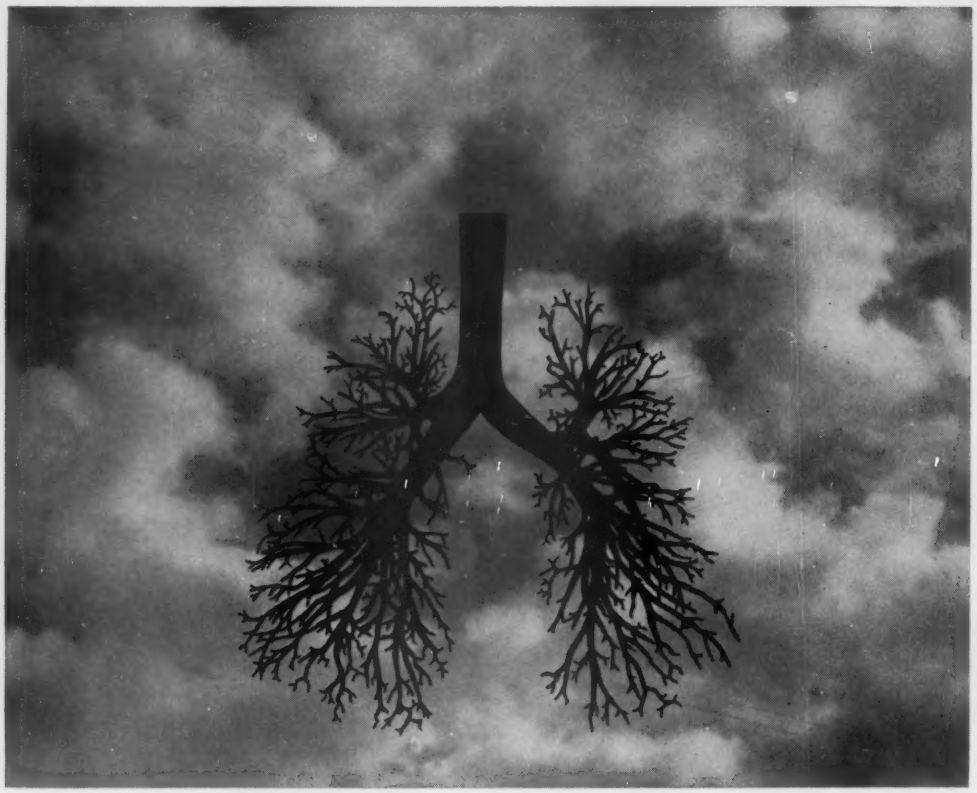

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Volume 253 AUGUST 18, 1955 Number 7

THE UTILITY OF THE BLOOD PEPSIN ASSAY IN CLINICAL MEDICINE

HOWARD M. SPIRO, M.D.,* ANNA E. RYAN† AND CHESTER M. JONES, M.D.‡

BOSTON

CONVENTIONAL study of gastric secretion is limited by several factors, including the effect of the tube in the stomach. Such an unpleasant procedure may stimulate or may inhibit gastric secretion; indeed, it may be so distasteful as to preclude passage of the tube. Therefore, re-emphasis on the fact that peptic activity in the urine reflects gastric secretory activity[1] stimulated much research into this more physiologic approach. Still, even urine collections were uncertain, and it was suggested that changes in water and electrolyte balance and in renal clearance might affect uropepsin excretion.

Mirsky et al.,[2] in 1952, described a method of assaying in the blood peptic activity that was believed to parallel gastric pepsin secretion. It is clinical experience with a new modification of their method that is reported in this paper, to show that the blood pepsin method has a place in the study of clinical problems.

PHYSIOLOGIC BACKGROUND

The chief cells of the gastric glands secrete pepsinogen, which is activated by the hydrochloric acid of the parietal cells to pepsin. Ninety-nine per cent of the pepsinogen granules are discharged into the gastric lumen, but about 1 per cent enters the blood,[3] where it may be assayed at an acid pH. From the blood, pepsinogen passes into the urine, where it is measured as uropepsin. Uropepsin is reported in terms of twenty-four-hour output; blood pepsin reflects the concentration of pepsin at a given interval only.

METHODS

Standard hemoglobin substrate is brought to a pH of 1.5 by the addition of 1 part of three-tenths normal hydrochloric acid to 3 parts of hemoglobin solution. To 10 cc. of this acidified substrate 2 cc. of plasma from oxalated blood and 3 cc. of distilled water are added to bring the total volume to 15 cc. and the final pH to 2.3. Two 6-cc. aliquots are measured: one is incubated at 37°C. for twenty-four hours; in the other, enzymatic digestion of the substrate is stopped at once by the addition of 10 cc. of three-tenths normal trichloracetic acid. After twenty-four hours the digestion is stopped in the first tube by trichloracetic acid. The amount of peptic activity in tyrosine equivalents split off from the substrate is then determined in both tubes by Anson's[4] method for a photoelectric colorimeter.

This method differs from that of Mirsky et al.[2] in that acidification is accomplished without the use of a pH meter, considerably simplifying the procedure for routine use. The pH for digestion by this method is 2.3, and that by the method of Mirsky and his associates 1.5; the concentration of hemoglobin substrate is slightly lower than in the original method. Therefore, our units are not equivalent to those of Mirsky et al., but the greater convenience and the increased ease of the procedure justify this change. Peptic activity is not appreciably different at pH 2.3 and at 1.5, so that the clinical significance is unchanged.

Mirsky and his co-workers[2] have shown that 150 to 200 of their units of proteolytic activity are extragastric in origin; by the present method, 100 units of activity or less are found in the plasma after total gastrectomy and therefore arise outside the stomach. In reports of results, this increment, which may well represent a contribution of cathepsin, is ignored, so that levels of 100 to 150 units indicate achylia. We have recorded all results above 850 as >850 because of the lesser accuracy in this range.

The method is reproducible in duplicate. Refrigerated plasma keeps well for forty-eight hours, but after three days there is an increasingly significant decrement in the readings. In normal subjects checked from day to day under standard conditions, there is a variation of about 10 per cent around a mean figure.[5]

Blood was usually drawn on the day after admission whenever possible, usually with the patient fasting. Gastric aspirations were done in certain cases, for corroboration, and analyses for pH, free acid and pepsin were carried out. In no case did

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knowledge of the blood pepsin level affect the patient's course, and later evaluation of each case, for this report, was made without knowledge of the blood pepsin level.

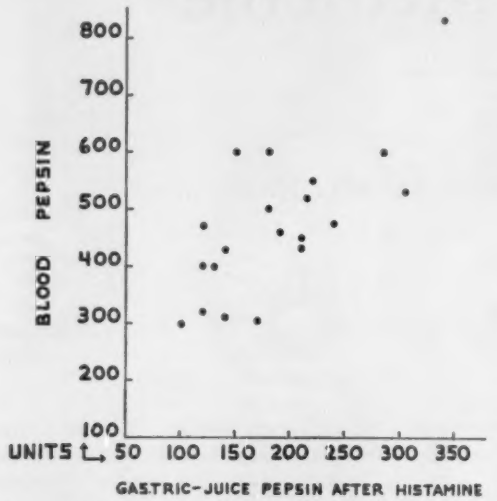

FIGURE 1. *Relation of the Blood Pepsin Level to the Gastric-Juice Pepsin Concentration.*

Each point represents a separate patient studied. The average blood pepsin level is plotted against the highest concentration of gastric pepsin "washed out" (but, of course, not stimulated) by histamine.

CLINICAL MATERIAL

All subjects, with the exception of a few ambulatory volunteers and some patients from the Outpatient Gastrointestinal Clinic, were hospitalized on the medical and surgical wards of the Massachusetts General Hospital. "Normal" patients, for these purposes, were those without known gastrointestinal complaints or disease. A special selection of normal subjects with gastrointestinal disease not involving the stomach was also made. All selection was at random, and only patients with generalized disease such as diabetes and uremia, or with very acute disorders such as myocardial infarction, were excluded. It seemed important not to use medical students or hospital personnel or "sidewalk" normal controls if the results were to have a meaning in clinical practice. Therefore, those "normal" subjects were not strictly normal, but were not significantly more or less ill than the patients with ulcer or other patients studied. Patients were accepted as having duodenal ulcer or other stomach disease only when there was good x-ray evidence.

RESULTS

There is little significant variation in the blood pepsin after meals, after small doses of insulin, or after histamine. Although no report is here made of the correlation between blood pepsin and actual gastric secretion, Figure 1 displays a probable direct relation between the preformed "washed-out" pepsin after histamine stimulation and the blood pepsin levels. No points are shown at achylia, nor is the relation to achlorhydria and achylia discussed, because of complicated factors involved that are at present under study.[5]

Normal Values

Figure 2 shows the spread of values in 146 "normal" patients selected at random. In Figure 2*A* no criteria other than the absence of upper digestive complaints are used. In Figure 2*B* all patients with disease anywhere in the gastrointestinal tract are excluded, with a consequent reduction in the number of subjects to 99. It is apparent that in Figure 2*A* there is a significant proportion of patients (46 or 31 per cent) with blood pepsin values above 400 units. After exclusion of patients with gastrointestinal diseases, the figure drops to 24 (24 per cent), but there are still many patients with levels of blood pepsin above 400 units. If 450 units is taken as the cut-off point, the number drops to 23 (15 per cent) in Fig-

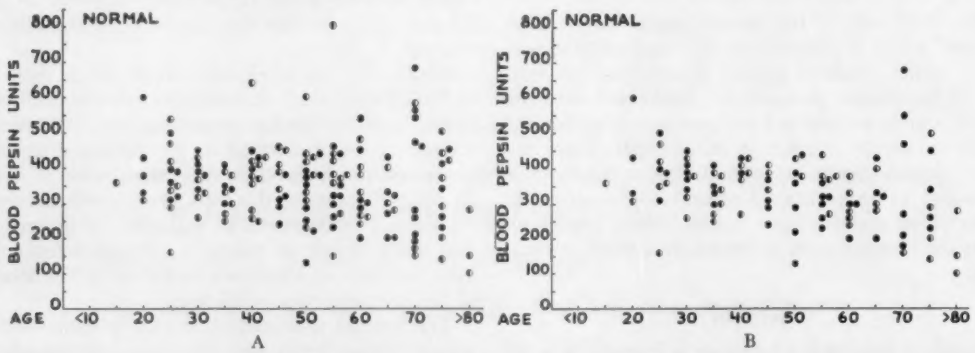

FIGURE 2. *Blood Pepsin Levels among Normal Subjects.*

A shows the spread of blood pepsin levels among "normal" hospitalized patients without stomach disease; some of the points represent patients with gastrointestinal-tract disease outside the stomach. In B *these points are excluded. Solid circles stand for men, and half-solid circles for women.*

ure 2*A* and to 9 (9 per cent) in Figure 2*B* above that figure. Below levels of 200 units in Figure 2*A* there are 13, or 9 per cent, of the subjects; in Figure 2*B*, there are 10 (10 per cent).

TABLE 1. *Median Blood Pepsin Values by Decades in "Normal" Patients and in Patients with Duodenal Ulcer.*

AGE	BOTH SEXES		MALES		FEMALES	
	MEDIAN BLOOD PEPSIN	NO. OF PATIENTS	MEDIAN BLOOD PEPSIN	NO. OF PATIENTS	MEDIAN BLOOD PEPSIN	NO. OF PATIENTS
decade	*units*		*units*		*units*	
"Normal" patients *without* known gastrointestinal complaints or disease:						
20	360	5	430	3	335	2
30	385	18	390	9	360	9
40	370	17	370	6	370	11
50	360	15	300	10	390	5
60	300	19	300	9	355	10
70	310	14	325	10	295	4
80	260	11	300	4	200	7
Totals		99		51		48
Average	336		345		329	
"Normal" patients *with* gastrointestinal disease not involving stomach:						
20	370	6	405	4	335	2
30	370	23	390	11	345	12
40	370	23	400	7	365	16
50	370	27	315	14	410	13
60	340	30	315	14	375	16
70	300	21	320	15	290	6
80	290	15	340	5	285	10
Totals		145		70		75
Average	353		357		343	
Patients with duodenal ulcer:						
20	680	4	680	4	—	0
30	565	6	565	6	—	0
40	660	11	680	7	635	4
50	570	21	570	17	545	4
60	550	20	565	12	520	8
70	540	25	540	19	505	6
80	575	10	575	8	650	2
Totals		97		73		24
Average	580		596		571	

in each age group are given in Table 1, together with the average for the entire group.

By cutting off the lower 5 per cent of patients and the upper 15 per cent, one arrives at levels of 150 to 450 units as the limits for 80 per cent of the "normal" patients.

Patients With Duodenal Ulcer

Figure 3*A* shows the spread of blood pepsin values in the patients with duodenal ulcer. In the group forty years of age and under (which may be too small for significance) none had levels below 400 units; a somewhat greater number of patients in the groups over fifty years of age — 16 (17 per cent) — had blood pepsin values below 450 units. Actually, below the age of forty, there was only 1 value below 500 units; all but 4 of these younger patients were males. Table 1 shows the medians and number of patients in each age group. Figure 3*B* indicates no change in blood pepsin levels with increasing duration of duodenal ulcer.

There was no observed change in the blood pepsin level during short-term clinical improvement of the patients with ulcer. After a few days in the hospital, an initially high level occasionally fell somewhat, but this was not a constant finding. The majority of subjects studied at an interval of six months to a year had values that were comparable to those during their hospitalization.

Patients with Gastric Ulcer

The small series of 20 patients with gastric ulcer (Fig. 4) demonstrates a wide spread of blood pepsin values. Of the 20 patients studied, however, 15 had values above 400 units, and 12 had values above 450 units. Only 25 per cent had levels below 400 units; 40 per cent had levels below 450 units. The average value for the group was 530 units, the median being 490 units.

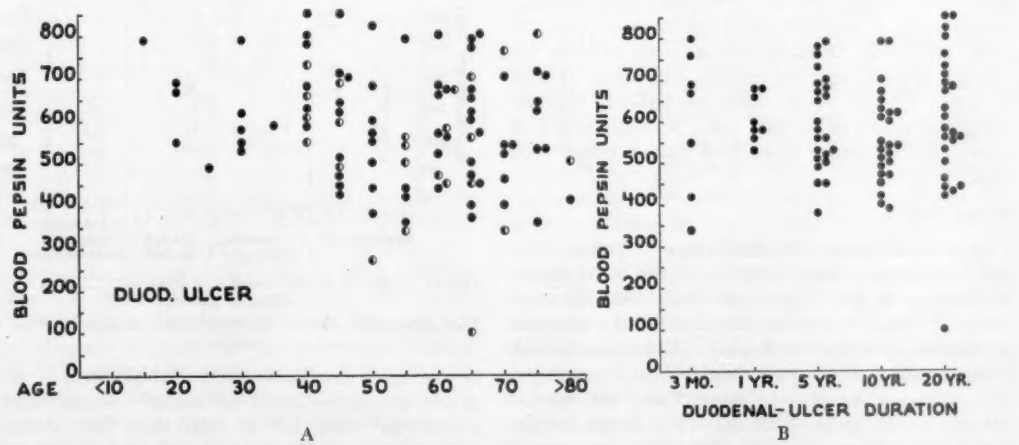

FIGURE 3. *Spread of Blood Pepsin Levels among Patients with Known Duodenal Ulcer* (A), *No Change in the Level Being Observed with Increasing Duration of the Disease* (B).

The data demonstrate a general drift of the blood pepsin levels downward with increasing age in normal people. The medians and number of patients

Patients with Gastric Cancer

Twenty-three patients with diagnosable gastric cancer were studied. Figure 4 shows that 43 per cent had values above, and 47 per cent values below

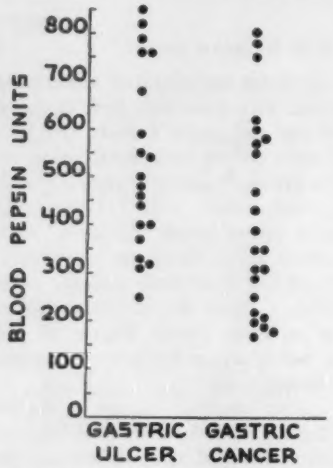

FIGURE 4. *Over-All Similarity in the Spread of Blood Pepsin Values in Patients with Gastric Ulcer and Those with Gastric Cancer.*

400 units. The average value for the group was 420 units; the median was 350 units.

Patients with Massive Gastrointestinal Hemorrhage

The helpfulness of the blood pepsin determination in 40 patients entering the hospital with massive gastrointestinal hemorrhage is demonstrated in Figure 5. The results of initial or average blood pepsin levels are arranged according to the final diagnosis. The average for the 18 patients with bleeding duodenal ulcer was 586, and the median was 250 units; for the 22 bleeding patients with cirrhosis the average was 277 and the median 250 units. It may be noted that 21 of the cirrhotic patients (95 per cent) had values below 400 units, whereas only 2 of those with duodenal ulcer had values below that level.

Hiatus Hernia

In a small group the association of peptic ulcer and hiatus hernia and the utility of the blood pepsin in diagnosis in such cases were evaluated. Figure 4 shows 19 patients studied, classified by the presence or absence of a duodenal ulcer. The patients with hiatus hernia but without duodenal ulcer averaged 323 units — somewhat lower than the normal average of 353 units. Patients with a hiatus hernia, esophagitis and a duodenal ulcer had an average level of 576 units.

Esophageal Stricture

Twelve patients with esophageal stricture were studied, and divided into two groups. One group was associated with peptic esophagitis and a known duodenal ulcer; the other comprised the end results of scleroderma, lye ingestion, postoperative stricture and the like. There were striking differences between the members of the two groups (Fig. 5).

Subtotal Gastrectomy

An effort was made to analyze, retrospectively but without knowledge of the blood pepsin levels, a group of 37 patients who had had a subtotal gastrectomy at least two years before this study. By "symptoms" (Fig. 5) are meant jejunal ulcer and bleeding, as well as incapacity because of "dumping" symptoms. A preponderance of patients with high levels of blood pepsin fell into the group with complications.

Discussion

The proposed modification for routine determination of blood pepsin is straightforward and reproducible. The levels are approximately constant in normal persons from day to day under standard conditions and satisfactorily approximate when measured over a period of months. It may be expected that changes in renal blood flow and in renal clearance may produce more variation than is here recorded. We have thus far found little variation postprandially, after histamine, or after insulin, which may result from a lack of sensitivity of the method. This corroborates the experience of Mirsky, Kaplan and Broh-Kahn[6] with uropepsin and of Chinn[7] with a blood proteolytic enzyme, presumably pepsin.

Within the limits of this clinical presentation, the blood pepsin level appears to be of value in *helping*

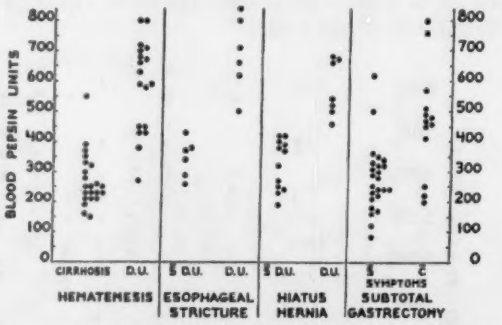

FIGURE 5. *Blood Pepsin Level as a Diagnostic Aid in Several Clinical States.*
The differences should be considered qualitative and not categoric.

to exclude a duodenal ulcer. A high level of blood pepsin activity — above 450 units — is suggestive of a duodenal ulcer, but no more than that; the large residue of "normal" patients with high blood pepsin levels prevents a more categorical attitude; whether duodenal ulcer is likely to develop in such cases is a matter of speculation and for patience. There may be unknown factors contributing to the high levels by an effect on the extragastric blood "pepsin." A

silent peptic ulcer was not excluded by x-ray study in most of these "normal" patients, but this fact should not detract from the clinical utility of the test. Unrecognized renal disease, which reduces renal excretion of pepsinogen, may conceivably have led to a retention of pepsinogen in the blood. Stress and anxiety played equally on the hospitalized normal subjects and on the patients with ulcer and therefore should have no urgent role. It may, however, be pertinent to note that several of the house staff ran blood pepsin levels in the upper range of normal (400 to 450 units) without any present digestive symptoms.

There may be a more impressive diagnostic utility of the blood pepsin in the groups forty years of age and under, but a much larger series of patients will be needed to confirm this. The lower values in the aging patients with duodenal ulcer probably represent a decay in gastric pepsin secretion similar to that more strongly indicated in the chart of the normal patients. The high levels of patients who have had an ulcer for more than twenty years is striking. There is complete lack of correlation between the duration of a duodenal ulcer and the blood pepsin level; this affirms the clinical susceptibility of the older age groups to recurrent duodenal ulcer.

The higher blood pepsin levels obtained when patients with digestive disease outside the stomach are included among the hospital "normal" subjects indicate that there may be a secretory effect of the other parts of the gastrointestinal tract on the stomach, but more direct studies are needed.

Two factors may have influenced the blood pepsin levels in the normal patients: if they had included, as they must in hospital practice, patients with acute diseases such as myocardial infarction the average levels would have been higher. If the normal controls had been limited to ambulatory, completely healthy persons from outside the hospital population the values might have been lower, but there could have been no valid comparison of blood pepsin levels for clinical purposes.

The blood pepsin level is of no worth in differentiating gastric ulcer from gastric cancer, since the spread of values in both is wide. The surprisingly large percentage of high blood pepsin values, which does not accord with reported experience with uropepsin,[8] in the patients with gastric ulcer deserves emphasis: it demonstrates that secretion may persist at a high rate, but that the reason for the usually low acidity clinically may lie with the buffers and mucus of the nonparietal secretion. Some of the highest blood pepsin values were found among the patients with gastric cancer, as was to be expected from the known variation in free acid among gastric cancers; it is entirely probable, however, that the blood pepsin level could be used as a screening test for achylia in an effort to pick up the achlorhydric precursors of gastric cancer.

The blood pepsin assay seems of great utility in the differential diagnosis of massive upper gastrointestinal bleeding, particularly in assuring the presence or absence of a duodenal ulcer. The rather low values of all the cirrhotic patients amplify the diagnostic difference between the two groups; it is surprising in view of the purported higher incidence of duodenal ulcer in cirrhosis. Our experience thus confirms the suggestion of Janowitz, Levy and Hollander[8] that the determination of uropepsin might be of diagnostic aid in hematemesis, and also indicates that a blood pepsin determination might be a worthy routine study.

In both hiatus hernia and esophageal stricture the consideration of the "acid-ulcer" diathesis as a factor is important: the presence of hypersecretion may predispose to the later formation of an esophageal stricture in patients with hiatus hernia because of regurgitation at the cardia. The expectation of good surgical results in such cases, the likelihood of recurrent stricture or the decision for medical treatment and bougienage may be based on the evidence for a duodenal ulcer as an early clue to this "ulcer diathesis." The blood pepsin assay as an indication of hypersecretion in these circumstances is apparent. Further experience *may* indicate that patients with high blood pepsin levels are not good candidates for surgery. The somewhat lower average values in patients with hiatus hernia alone may be the result of gastritis in the hernial sac and may indicate progressive destruction of the pepsinogen-secreting mechanism.

The group of patients with old subtotal gastrectomies is presented purely tentatively. One would have expected more bleeding but less "dumping" among patients with high postoperative blood pepsin levels, but thus far experience shows both "dumpers" and bleeders in this group. Shay[9] has recently reemphasized the necessity for evaluating the gastric acid secretion in the stomach remnant in this regard. Patients with such high postoperative levels may well be considered candidates for further ulcer complications, since the blood pepsin level is a clear index of the amount of secreting gastric mucosa remaining.

In any event the blood pepsin level reflects the integrity of one facet of gastric secretory activity, uncontaminated and unstained with bile. It cannot replace gastric aspiration as a measure of the end result, in the stomach lumen, of the mixture of acid and pepsin with food and with nonparietal secretion. Although its relation to uropepsin excretion appears to be a direct one the present studies do not parallel, as far as the blood pepsin level is concerned, the recent suggestion[10] of an absolute diagnostic value to the uropepsin excretion. The relation between uropepsin and blood pepsin is in need of further exploration, but at present we believe that the blood pepsin assay is superior in ease of obtaining samples, daily reproducibility and ease of determination. Our studies indicate its worth in clinical practice.

Summary

A modification of the method for blood pepsin determinations devised by Mirsky and his associates is presented. The utility of this assay in the exclusion of duodenal ulcer, in the evaluation of the ulcer diathesis and its possible clinical importance in the differentiation of peptic esophagitis and stricture from that unassociated with hypersecretion is examined. It is concluded that the blood pepsin measurement should be a useful clinical test.

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THERAPEUTIC FACTORS IN SURVIVAL AFTER LETHAL CHOLINESTERASE INHIBITION BY PHOSPHORUS INSECTICIDES*

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THE purpose of this paper is to acquaint the clinician with the intoxication produced by some of the commonly used phosphate insecticides, the material being based on a survey of the severe and fatal cases that have occurred since their use was introduced several years ago.

Accidental poisoning with organic phosphoric acid esters has been of profound interest in these laboratories since it was learned in 1946 that the Germans had adapted such compounds to military use in the form of highly toxic, volatile and almost odorless nerve gases. Similarities in biologic effects and chemical structure between these insecticides and nerve gases have stimulated extensive studies with a view to understanding all aspects of intoxication with them.[1] This effort is intended to provide optimum defense against their military use as well as to collect data that might be useful to investigative medicine, in treatment of disease and in the care of workers in agriculture and in insecticide plants.

Parathion (p-nitrophenyl diethyl thionophosphate) and tetraethylpyrophosphate have been the most commonly used insecticides, particularly the former.[2] Tons are sprayed annually both from the ground and by airplane. Nevertheless, accidental poisoning has been limited almost entirely to persons in direct contact with the materials, such as mixers and sprayers in the field and workers in insecticide plants.[3,4] Occasionally, children have come upon containers of insecticide by chance, but unwary neighbors have rarely been affected through air pollution.[5] Accidental airplane crashes, involving pilots who had been spraying crops with phosphorus insecticides, were thought to have resulted from mild poisoning.[6]

The liquid organic phosphates vary in terms of volatility and solubility, and these factors determine both their usefulness and toxicity.[2] Tetraethylpyrophosphate is highly toxic, water soluble but rapidly hydrolyzed in aqueous solution. Therefore, it is a relatively nonpersistent insecticide and has been responsible for acute, fulminating intoxication in accidental exposure.[7-9] Parathion is relatively nonvolatile, insoluble in water and, by weight, about a tenth as toxic as tetraethylpyrophosphate.[10] In addition, parathion is oxidized in vivo to its active anticholinesterase analogue, paraoxon, thus delaying the onset of symptoms.[11]

Development of clinical intoxication is slower with parathion than with nerve gas or tetraethylpyrophosphate, rates being dependent largely on probable routes of absorption and dose. Tetraethylpyrophosphate is intermediate in toxicity between nerve gas and parathion.

The effects of these compounds depend almost exclusively upon their selective inhibition of cholinesterases.[12,13] These are hydrolyzing enzymes responsible for maintaining proper concentrations of acetylcholine, which mediates nerve impulses in the central nervous system, in autonomic ganglions and at parasympathetic and neuromuscular end organs. Thus, acetylcholine controls ultimate cholinergic functions. The primary disease, therefore, is one of poisoning with acetylcholine complicated by its sequelae, the most serious of which is respiratory distress with anoxia and subsequent death. Clinical poisoning is not known to affect biochemical systems other than that of cholinesterase and the substrate, acetylcholine.[14]

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Earlier clinical studies of organic phosphorus insecticide poisoning by Grob et al.[3,13] represent the basic ones in this field. Since then, a considerable number of acccidents have occurred.

This paper summarizes available experience with severe cases to date and the comparative results of treatment.

The study of the pathogenesis and effects of treatment in severe poisoning was made possible through the co-operation of numerous physicians, chemical houses and governmental agencies. The value of these observations was inestimably enhanced by experience in the laboratory and with mild and occasionally serious accidents with nerve gas in the Chemical Corps. Only patients judged by clinical criteria to have absorbed lethal doses, whether or not they survived, are included. Twenty-three of 41 patients poisoned with parathion and none of 5 poisoned with tetraethylpyrophosphate recovered (Table 1).

It can be expected that rate and total amount of absorption would ultimately depend on the duration and area of body surface in contact with a particular compound. Permeability would be related mainly to solubility characteristics in the skin and to superficial blood flow in the contaminated parts. Although the skin has been the major route of entry for both compounds, contamination of the oronasal mucous membranes, upper respiratory tract and conjunctivas with particles, aerosols and vapor must have been inevitable during dispersal by spray. The relatively slow absorption from skin leads to insidious changes so that the uninitiated may remain disarmed, owing to mildness of symptoms, whereas the prepared person may be forewarned to good advantage.

TABLE 1. *Distribution of 46 Cases of Fatal Poisoning According to Survival and Toxic Compound.*

COMPOUND	SURVIVALS	DEATHS	TOTALS
Parathion	23	18	41
Tetraethylpyrophosphate	0	5	5
Totals	23	23	46

CLINICAL OBSERVATIONS

Characteristically, on the day of illness the worker has been spraying his orchard or field for several hours without recommended protective measures. Usually, he manages to have his noon meal and returns to work. Shortly afterward symptoms of poisoning (Table 2) are likely to appear. He is nauseated, dizzy and lightheaded and may vomit. Within the next hour or two the extent of severity becomes manifest. If the poisoning is severe, the speed and skill of management after the first hour will determine the outcome.

Contact with skin exaggerates sweat-gland activity, and there may be local twitching and fasciculation. Other local effects are blurring and dimness of vision because of absorption through the eyes, with subsequent ciliary spasm causing marked constriction of the pupils and impaired accommodation. Rhinorrhea and sensations of tightness or pressure in the chest and, occasionally, coughing are sometimes noted and are probably due to local effects on the mucous membranes. Local effects have been of little consequence, except, perhaps, to pilots in terms of visual acuity.

TABLE 2. *Symptoms and Signs of Parathion Poisoning in the Usual Order of Development.*

Nausea	Muscle twitching	Incontinence
Headache	Inco-ordination	Random, jerky movements
Vomiting	Slurred speech	Increasing respiratory difficulty
Dizziness	Confusion	Cyanosis
Weakness	Difficulty in breathing	Convulsions
Sweating	Hypertension	Coma
Abdominal cramps & diarrhea	Excessive respiratory mucus	Failure of breathing
Miosis	Oronasal frothing	Failure of blood pressure
Dim or blurred vision	Stupor	Death

However, as the insecticide becomes absorbed, the cholinesterase of both the plasma and the red cells becomes inactivated. When the rate of absorption exceeds the capacity of blood cholinesterase to react with it, inhibition of the enzyme in tissues probably follows.[3] A slow rate of absorption may result in almost complete inhibition of blood cholinesterase without affecting tissue esterase, as though blood were a protective barrier.[16] The role of cholinesterase in blood has not been clarified, but its presence there does not appear to be essential to life. Inhibition of tissue cholinesterase, on the other hand, is thought to give rise to a definite series of events.

Nausea is followed by vomiting, and there may be abdominal cramps and diarrhea. Dizziness, and perhaps headache, may coincide with general weakness. Soon there are likely to be spontaneous twitchings of muscles. Mental confusion, slurring of speech and disorientation set in, the gait becomes clumsy and staggering, and random involuntary movements of the arms occur and generally are followed by major convulsions. Meanwhile, sweating has become profuse, and breathing rapid, shallow, and sometimes, irregular. Stupor and, finally, coma ensue. Breathing becomes noisy as secretions are poured out of salivary, serous and mucous glands of the mouth and respiratory tract. Froth wells up into the oropharynx and nasopharynx. The skin and mucous membranes turn cyanotic as breathing becomes shallow and halting and finally stops. The blood pressure has climbed to abnormal levels as asphyxia has become intense. Circulation is maintained for some time after apnea develops. Widespread rales and rhonchi are heard on examination. Then deterioration is rapid, and

death ensues from anoxia and circulatory collapse.

Respiratory failure, the critical factor in survival, results mainly from intoxication of the respiratory centers and paralysis of the thoracic musculature and diaphragm. Mechanical obstruction to airflow is due to the viscid secretions from the submucous glands and goblet cells of the respiratory epithelium. Spasm of peribronchial smooth muscle, engorgement of the pulmonary circulation and some edema of the pulmonary tissue and alveoli are additional burdens to failing respiration.

TABLE 3. *Estimated Minimum Red-Cell Cholinesterase Activity after Lethal-Type Intoxication in 14 Cases of Parathion and Tetraethylpyrophosphate Poisoning.*

RESIDUAL CHOLINESTERASE	PARATHION		TETRAETHYL-PYROPHOSPHATE
	NO. OF SURVIVORS	NO. OF FATAL CASES	NO. OF FATAL CASES
%			
<20	10	1	—
>20	1	1	1
Totals	11	2	1

Hyperstimulation of cholinergically innervated tissue has been substantiated by histologic evidence, after death, suggesting hyperactivity of serous and mucous glands of the respiratory tract. Secretions from these and unusually prominent goblet cells tend to fill the secretory ducts and adjacent airways even within the few minutes of life after ingestion of tetraethylpyrophosphate.[9]

The criteria for distinguishing potentially fatal cases were derived from 90 cases of varying degrees of intoxication. Lethality was predicated on the similarity of signs, rates of development and degrees of intoxication before treatment. Respiratory inefficacy, generally associated with cyanosis, and serious, generalized impairment of the nervous system characterized the fatal cases before treatment. Thus, patients who might have died except for fortuitously favorable circumstances could be recognized with reasonable confidence and distinguished from those who would have survived regardless of treatment.

CHOLINESTERASE

Red-cell cholinesterase activity was determined in 1 case of tetraethylpyrophosphate and 13 of parathion poisoning. Of the latter, 11 determinations were in survivors, and 2 in fatal cases. Cholinesterase levels had been measured by various technics and at variable periods after the onset of poisoning. Rough estimates of maximum depression were calculated on the basis of the uniform rate of new red-cell generation and longevity, the rate of enzyme recovery being proportional to the greatest degree of its inhibition.[16] Cholinesterase inhibition may be reviewed roughly as shown in Table 3. For the most part, the degree of cholinesterase inhibition was compatible with the clinical impression of lethal intoxication.

Other factors thought to have been important in determining the outcome in individual cases were evaluated according to clinical judgment. To describe the 23 survivors and 23 fatal cases among the 46 persons poisoned with lethal doses of parathion and tetraethylpyrophosphate the cases were placed in several general classifications (Table 4).

THERAPEUTIC FACTORS

The most effective therapy was characterized by 10 cases of parathion poisoning in which treatment, with both atropine and oxygen (or artificial respiration), was administered early, adequately and continuously, so that there was little doubt about reversibility of the pathologic process and recovery. In the next most favorable group of 7, the early effort at treatment with atropine was inadequate, but it delayed the rate of clinical deterioration so that successful dual measures (atropine and ventilation) could be taken later, usually in a hospital. A group of 3 patients received atropine alone in adequate amounts, and the pathogenesis was successfully reversed. In 1 case intoxication had advanced to a dangerous point because treatment was not available until late. Then, the vigorous application of both atropine and artificial respiration reversed the trend and resulted in survival. In another case oxygen was the main therapeutic measure, but small, timely doses of atropine appeared to be significantly supportive. Another patient was given manual artificial respiration alone for the apneic state, after tracheotomy, and survived.[17]

TABLE 4. *Classification of Treatment (Atropine and Ventilation) among 46 Cases of Lethal-Type Poisoning and Outcome in Terms of Survival.*

TYPE OF TREATMENT	NO. OF CASES	SURVIVORS
Dual treatment, early & adequate (atropine combined with artificial respiration or oxygen)	10	10
Palliative atropine, followed by delayed adequate treatment	7	7
Early & adequate atropine, alone	3	3
Dual treatment (atropine combined with artificial respiration or oxygen) late but vigorous	1	1
Oxygen treatment mainly, with token atropine	1	1
Tracheotomy & manual artificial respiration	1	1
Initially effective atropine, without adequate maintenance	5	0
Atropine or ventilatory treatment, late & inadequate	8*	0
None	10†	0
Totals	46	23

*Includes 2 cases of tetraethylpyrophosphate intoxication.
†Includes 3 cases of tetraethylpyrophosphate intoxication.

Negative results included 5 cases of tetraethylpyrophosphate poisoning described below. Five patients poisoned with parathion improved with atropine, at first, but relapsed and died, evidently because of

inadequate maintenance of atropine. In 6 cases the earliest administration of atropine was very late, and too little was given to have been effective in these advanced stages. Seven patients had not been treated.

The rate of development of intoxication with tetraethylpyrophosphate was usually rapid (Fig. 1). Of 5 cases intoxication in 3 was by ingestion. The patients died too soon for help to have been sought. The other 2 occurred in children who played with the material, and intoxication developed more slowly after its absorption through the skin. There was time for them to be taken to physicians, but delay in 1 case apparently allowed irreversible anoxic damage to the brain. Spontaneous breathing was resumed but could not support life beyond two days. In the other case, timely administration of oxygen failed because of obstruction of the airway and in spite of laryngeal intubation.

Atropine

Ten out of 12 patients with fatal parathion poisoning survived for at least five hours after the onset of

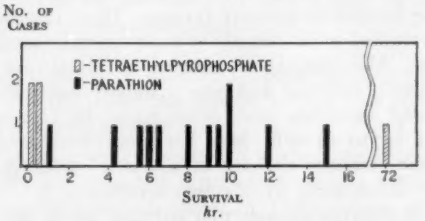

Figure 1. *Length of Survival after Onset of Symptoms in 17 Fatal Cases (12 from Parathion and 5 from Tetraethylpyrophosphate).*

symptoms. With this survival period as a baseline therapy during the equivalent five hours among the survivors was compared. In terms of atropine, survivors were treated earlier than patients who died; also, the total amount administered during the first five hours was greater than that in the fatal cases (Fig. 2 and 3). Survivors received atropine, initially, in an average time of an hour and twenty minutes after onset (Fig. 2) whereas the average interval was three hours, or about twice as long, in the fatal cases. Survivors had received about four times as much atropine (an average of more than 3 mg. rather than less than 1) during the first five hours (Fig. 3). There was wide variability.

Respiratory Resuscitation

So far as respiratory insufficiency is concerned serious interference with air exchange, or apnea, would lead to death shortly. In this regard atropine was highly effective both in minimizing intoxication of the respiratory centers and in controlling hypersecretion from the glands of the respiratory submucosa and goblet cells, the major factors that led to death from anoxia. Repeated aspiration was generally necessary to maintain a patent airway. To be sure, when atropine alone had not re-established ade-

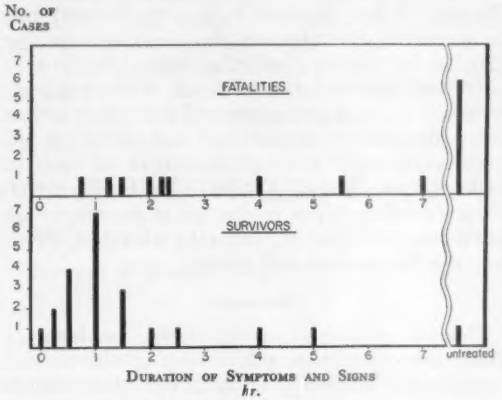

Figure 2. *Duration of Symptoms and Signs before Initial Administration of Atropine in 15 Fatal Cases and 22 Cases of Survival after Parathion Poisoning.*

quate ventilation, breathing was maintained or restored either by manual compression of the chest or by means of a mechanical respirator. Oxygen was supplied variously by the aid of masks, tents, nasal

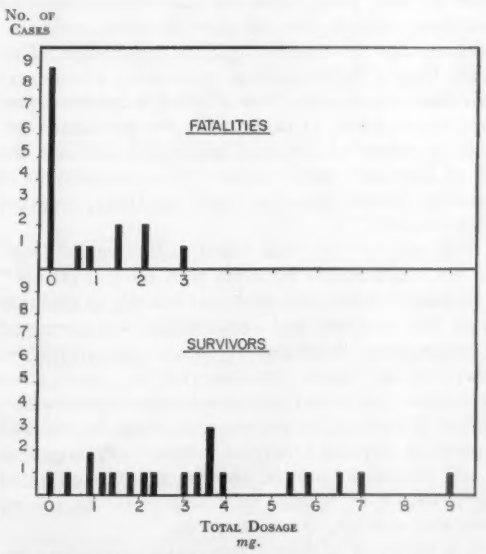

Figure 3. *Total Amount of Atropine Administered during the First Five Hours of Intoxication in 16 Fatal Cases and 20 Cases of Survival after Parathion Poisoning.*

catheters and intratracheal tubes to restore favorable partial pressures.

In addition to atropine adjunctive measures may be essential for the successful management of potentially lethal intoxication. Aspiration of mucus through a rubber catheter and syringe may be ineffective so that endotracheal intubation may be

required in the absence of a mechanical aspirator. Neither aspiration nor insertion of airways appears to be feasible without relaxation of the lower jaw and pharynx. Other measures failing, tracheotomy may be necessary. Dehydration, the result of vomiting, diarrhea and excessive sweating, should be treated by parenteral administration of fluids, with careful observation to avoid precipitation of pulmonary edema. Acute disturbances in acid-base and electrolyte balance may occur.[18] Although reversal of the basic intoxication was generally followed by rapid recovery from secondary effects proper use of electrolytes administered, with guidance from the laboratory, should improve the outlook still further.

Discussion

General physiologic deterioration, resulting directly from cholinergic stimulation, as well as from anoxia, has ultimately affected the cardiovascular system, leading to circulatory failure. Intoxication with respiratory embarrassment has been accompanied generally by hypertension, which improved with relief of anoxia or fell with ultimate circulatory collapse. Among the essential factors in controlling the sequelae of cholinesterase inhibition the blocking of cholinergic phenomena with atropine seems to have been the simplest and most effective. It appears to have been easier to maintain spontaneous breathing through the effective blocking action of atropine than to employ artificial respiration alone in the face of hypersecretion, pulmonary edema and convulsive movements. Nevertheless, it has been possible, on occasion, to support life for protracted periods by means of artificial respiration, without the use of atropine, until cholinergic overstimulation of secreting glands subsided and breathing recurred spontaneously.[17]

It is well to note that blood cholinesterase levels did not continuously correlate with clinical effects.[15] A reasonable relation existed only initially as cholinesterase was inhibited and acetylcholine was permitted to accumulate. Subsequently, either spontaneous regeneration of tissue cholinesterase or some other mechanism permitted acetylcholine to come under control so that physiologic processes could be resumed in spite of depressed enzyme activity.[3] Pathogenesis is also related to rate of absorption, extreme blood cholinesterase depression, accumulated slowly, having been seen with negligible symptoms.[6,15,16]

It is pertinent to discuss two major distinctions between man and the more commonplace laboratory animals in terms of response to intoxication. One is severe hindrance to breathing in dogs caused by bronchoconstriction that is relieved by atropine.[19] In man clinical evidence has not indicted bronchoconstriction, per se, as a major factor in respiratory distress. It appears, on the other hand, that inactivation of the respiratory centers and neuromuscular end organs, combined with hypersecretion, is more disabling than bronchoconstriction.

The second major distinction has been rapid inhibition of intracardiac conduction in animals by cholinergic stimulation. Heart block increases rapidly until ventricular rates are reduced fourfold to sixfold.[10] Man has given no overt evidence of intracardiac block. However, such an influence has been suggested by the failure of cardiac rates to rise above 80 to 100 per minute in the face of severe asphyxia in some cases. This implies that, in man, relative, rather than absolute, bradycardia may develop.

Summary and Conclusions

Intoxication with lethal doses of phosphorus insecticides, or of nerve gases, generally can be contained and reversed with treatment applied early and vigorously. The efficacy of atropine in blocking and reversing the toxic action of excessive acetylcholine has been remarkable. It not only has controlled the protean respiratory and central neural manifestations of poisoning but also has strikingly facilitated administration of air (or oxygen) when breathing failed. It appeared to relieve the mechanical obstruction caused by hypersecretion, and allowed recovery of the blocked respiratory centers. Thus, respiration was resumed spontaneously or maintained by artificial means. Also, mechanical clearing of the airways was frequently essential and was managed generally by repeated aspiration and, occasionally, by intubation of the larynx as well. Man has been resuscitated on occasion without the aid of atropine, although lethally intoxicated, by effective ventilation.

Data indicate strongly that atropine, given promptly in quantities greater than 3 mg. within the first five hours (while circulation is still efficient) and continued as necessary, is likely to revive persons severely poisoned with parathion. Supportive ventilation must be included as indicated. Rapid poisoning by more toxic and volatile materials, such as tetraethylpyrophosphate and nerve gases, requires more prompt and vigorous measures of the same type.

We are indebted to the many physicians who have made this survey possible through their generous provision of records, post-mortem material and considerable time.

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CONGENITAL CARDIAC MALFORMATIONS IN THE NEONATAL PERIOD*

An Autopsy Study

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IN a recent study[1,2] from New York of 5964 pregnancies with 6053 births, 433 products of conception, or 7.5 per cent, were found to have congenital malformations. These malformations were classified by systems, and 50 of the 6053 babies, or 0.83 per cent, had malformations of the cardiovascular system. When the rate was calculated in relation to age at the time of death, cardiovascular malformations were present in 7.7 per cent of infants who were either stillborn or who died within the first month, but this fell to 0.6 per cent in infants who survived for more than a month.

The purpose of the present study is to survey and classify the anatomic types of congenital cardiovascular malformations found in 100 newborn infants autopsied at the Boston Lying-in Hospital from 1931 through 1954, and to compare the observations on newborn infants with those found in persons dying of congenital heart disease at all ages. During this period over 100,000 babies were born at this hospital; the files contain records of 1665 autopsies on viable fetuses, stillborn infants and infants who died in the neonatal period. During the period in question, autopsies were performed on about 60 per cent of the infants who died in the first month. In 100 of the 1665 autopsies a congenital cardiovascular malformation was present, an over-all rate of 6.0 per cent. These data do not include infants born with congenital cardiac malformations evident at birth who were transferred to other hospitals for treatment or who were well enough to be discharged to the custody of their parents and the care of their pediatricians. Cases in which a clinical diagnosis of congenital heart disease was made and in which the infant died at the Boston Lying-in Hospital but was not autopsied are also excluded. If, to lend perspective to these figures, the New York rate of 0.83 per cent is applied to the 100,000 births at the Boston Lying-in Hospital there is a hypothetical prevalence of 830 cases of congenital cardiovascular malformation; in these an unknown number of infants survived or died without autopsy, but 100, or 12 per cent, died within the first month and were autopsied. The anatomic classification of these 100 cases is given in Table 1. Each case is counted once and is

TABLE 1. *Congenital Cardiac Malformations among 100 Consecutive Autopsies at the Boston Lying-in Hospital (1931-1954).*

MALFORMATION		No. OF CASES
Transposition of the great vessels		27
Complete, without intracardiac shunt	13	
Complete, with interventricular septal defect	9	
Complete, with interatrial septal defect	1	
Partial, with interventricular septal defect	2	
Partial, with interatrial septal defect	1	
Interventricular septal defect		19
Uncomplicated by other cardiac lesions	6	
Associated with other cardiac lesions	9	
Associated with extracardiac congenital anomalies	4	
Complete defects of cardiac septums		12
Cor triloculare biventriculare	1	
Cor triloculare biatriatum	6	
Cor biloculare	5	
Coarctation of aorta		11
Infantile type	6	
Adult type	3	
Coarctation of arch or ascending aorta	2	
Endocardial sclerosis (fibroelastosis)		7
Interatrial septal defect		6
Tetralogy of Fallot		4
Persistent truncus arteriosus		4
Miscellaneous		10
Idiopathic cardiac hypertrophy	3	
Bicuspid aortic valve	2	
Anomalous aortic arch	1	
Mitral & aortic stenosis, with left ventricular hypoplasia	1	
Pulmonary atresia, uncomplicated	1	
Malrotation of heart (associated with multiple anomalies)	1	
Mongolism, with multiple cardiac anomalies	1	
Total		100

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classified under the major anomaly present; associated anomalies are specified as indicated.

Distribution of Malformations

The frequency distribution of anatomic lesions (Table 1) is best understood in the perspective of Abbott's[3] tabulation of the type of congenital cardiac malformation in 1000 autopsied cases that included not only the neonatal period but also patients dying in infancy, childhood and adult life. This comparison is presented in Table 2, in terms of the percentage of each type of lesion as the primary defect. The comparison for the more frequently encountered lesions is shown graphically in Figure 1. This comparison shows that the most frequent cardiac causes of death during the first month of life are transposition of the great vessels and defects in the interventricular septum; if cor biloculare and cor triloculare are included with this group the rate of occurrence of such defects becomes 30 per cent in this series and 9.9 per cent in Abbott's[3] series. The ratio between this series and Abbott's series regarding both transposition of the great vessels and defect of the interventricular septum, partial or complete, is 3:1.

Table 2. *Comparison of Anatomic Types of Congenital Malformation in 100 Patients Dying in the Neonatal Period and 1000 Dying at All Ages.*

Type of Congenital Cardiac Malformation	Percentage in Present Series	Percentage Reported by Abbott[3]
Transposition of great vessels	27	8.1
Interventricular septal defect	19	6.2
Cor triloculare & biloculare	12	3.7
Coarctation of aorta	11	8.5
Tetralogy of Fallot	4	15.0*
Patent ductus arteriosus	0†	10.5
Endocardial sclerosis (fibroelastosis)	7	0
Interatrial septal defect	6	7.6‡
Persistent truncus arteriosus	4	3.0
Anomalies of pericardium	0	3.6
Displacement of heart	1	4.4
Anomalies of semilunar cusps	2	4.4
Idiopathic cardiac hypertrophy	3	1.5
Other	6	23.5§

*Enumerated as pulmonic stenosis and pulmonary atresia.
†Not defined as anomalous in neonatal period.
‡Includes patent foramen ovale.
§Includes many types of anomaly not causing death in the 1st month.

Abbott's 1000 cases include 120 patients (12 per cent) who died within the first month of life. Although her series was accumulated from a large number of individually reported cases and is somewhat weighted on the side of unusual anomalies, the most frequently enumerated lesions in infants dying within the first month were as follows: transposition of the great vessels, 16 cases (13.3 per cent); aortic stenosis and atresia, 16 cases (13.3 per cent); anomalies of the aortic arch, 7 cases (5.8 per cent); coarctation of the aorta, 10 cases (8.3 per cent); and so-called aneurysm of the ductus arteriosus, 10 cases (8.3 per cent). The figures given in Table 2 include these cases; if they are excluded the contrast in distribution of types of lesion in relation to age of survival is even more striking. It is of some importance that corrective surgical procedures for the two most frequently encountered lesions in Abbott's tabulation — patent ductus arteriosus and the tetralogy of Fallot — have subsequently been devised.

In the present series there were conspicuously few lesions involving the pulmonic valve and the aortic valve. The low rate of occurrence of isolated pulmonic stenosis is explained by the fact that infants with this lesion (estimated by some to be among the most frequently encountered cardiac malformation) survive beyond the first month of life almost without exception. One case in which the aortic valve was almost completely stenotic, this being the only lesion found, was classified as endocardial sclerosis on histologic examination. In 2 other cases of endocardial sclerosis the aortic valve was thickened and stenotic, but mural lesions of fibroelastosis were present. In 2 cases classified as coarctation of the aorta there was narrowing of the ascending aorta, with reduction in caliber of the aortic valve. Both Abbott[3] and Potter[4] found malformations involving the aortic valve and arch to be much more frequent.

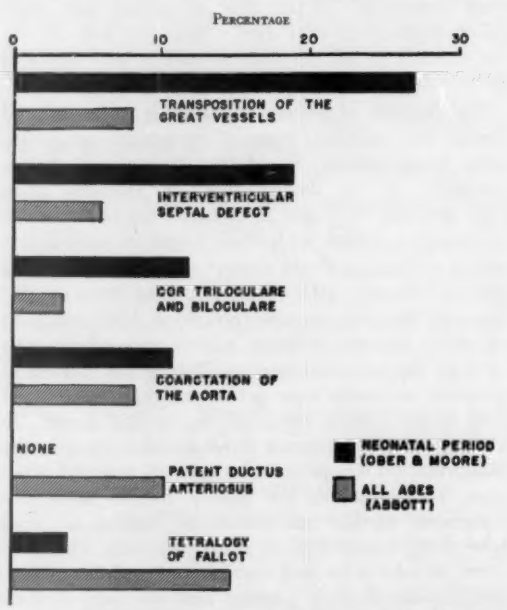

Figure 1. *Comparison of the Frequency of the Common Types of Congenital Cardiovascular Malformation in Infants Dying within the First Month (100 Cases) and in Those Dying at All Ages (1000 Cases).*

Sex

Of the 100 infants studied, 64 were male, and 36 were female, a ratio of almost 2:1. In only two of the types of lesion was there any significant sex preponderance. Of the 13 cases of complete transposition of the great vessels, without other cardiac anomalies, all the cases occurred in male infants. This male preponderance corresponds with that observed by Keith et al.[5] as well as others. Of the 7 cases of endocardial sclerosis 6 occurred in male infants, and 1 in a female infant. Craig[6] observed a similar predilection for males.

Age

Of the 100 infants studied 9 were stillborn, 70 died within the first week of life, 9 died in the second week, 8 in the third week, and 4 in the fourth week. Increased survival within the first month did not tend to be associated with any particular type of malformation. Of the 9 stillborn infants 4 had multiple congenital anomalies involving other systems than the cardiovascular.

Stillbirths

The 9 stillborn infants in this series included 4 males and 5 females. The most common cardiac lesion was a large defect in the interventricular septum, which was the primary lesion in 5 cases; tetralogy of Fallot was present in 2 cases, and coarctation of the aorta and endocardial sclerosis were found in 1 case each. Four of the stillbirths were in premature infants, who weighed from 1150 gm. to 1860 gm.; the others were at or near term. Four of the stillbirths were associated with multiple congenital anomalies of other systems. One of the cases of stillbirth was in a female infant who had a 10-mm. defect at the base of the interventricular septum. No other cardiac lesions were present, nor was any other anomaly found. The heart weighed 45 gm. One must either interpret this as an idiopathic cardiac hypertrophy associated with the defect or else infer that the increased heart weight represents work hypertrophy of the malformed fetal heart *in utero*.

Multiple Congenital Anomalies

Seven infants, including 4 who were stillborn, exhibited severe anomalies of other systems in addition to a major cardiovascular malformation. None of the 3 liveborn infants survived for more than twelve hours. In this group 4 were males, and 3 were females. The most common cardiac malformation was a large defect of the interventricular septum, present in 5 of the 7 cases. It was associated with genitourinary malformations alone in 2 cases, with central-nervous-system malformation alone (meningocele and hydrocephalus) in 1 case, and with combined renal and central-nervous-system malformations in 2 cases. One of the remaining 2 cases was in an infant of a diabetic mother; it had malrotation of the heart, malrotation and partial atresia of the bowel and multiple splenic nodules. The other was a case of tetralogy of Fallot with craniorachischisis, cyclopia, absence of the hypophysis, hemangiomatosis of the central nervous system and a large diaphragmatic hernia on the left. In addition to the 7 infants listed above, there was a case of mongolism in the series. This infant was born at term to a forty-three-year-old mother whose only previous child, born three years before, was normal. The infant succumbed at five hours with cyanosis, gallop rhythm and dyspnea. Autopsy revealed a 3800-gm. male infant with the external stigmas of mongolism. The only malformations were in the cardiovascular system, where they were multiple and *sui generis*, including patent foramen primum, a defect of the interventricular septum, common atrioventricular valve, persistent left cardinal vein and coarctation of the aorta of the infantile type.

Association of Cardiac Lesions

During the course of this survey it became apparent that certain types of malformed hearts, although classified according to the major lesion present, merited specific attention because of the distribution of the lesions or their association with other anomalies within the heart. Of the 11 cases classified as coarctation of the aorta, 6 were of the infantile type, with the coarcted segment proximal to the ductus arteriosus, 3 were of the so-called adult type, with the coarcted segment distal to the ductus arteriosus, and 2 represented coarctation of the ascending aorta and arch respectively. The ductus arteriosus was patent in all these cases. Examination of the clinical records showed that almost all these infants died in congestive heart failure.

The distribution of lesions in the cases of endocardial sclerosis conforms to Craig's[6] observations. In 5 cases the lesion was on the left side; 3 of these patients had involvement of the aortic valve, mitral valve and left mural endocardium; 1 case showed involvement of the aortic valve and left mural endocardium, and in 1 case the lesions were confined to the aortic valve, producing a complete stenosis. In 2 cases the lesions were on the right side; in 1 of these the fibroelastosis involved the pulmonic valve and right ventricular endocardium; in the other case the fibroelastosis was confined to the tricuspid valve and the immediately subjacent endocardium; there was an associated narrowing of the pulmonary artery and a small defect of the interventricular septum in this case.

Analysis of the cases classified as defect of the interventricular septum showed that in 6 cases this was the only lesion present; it was associated with other cardiac anomalies in 9 and with multiple con-

genital anomalies in 4 cases (as discussed above). There was no consistent pattern of association in the 9 cases: 1 patient had a bicuspid pulmonic valve; another had a bicuspid aortic valve; atresia of the pulmonary artery and dextrocardia were present in 1 case; in another there was isolated moderate stenosis of the pulmonic valve; and in still another there was isolated moderate stenosis of the aortic valve. In none of these did the associated lesions seem to contribute so much to the clinical course as the septal defect. However, in 4 cases, the association of lesions may have had significance in relation to the hemodynamic pattern: 1 patient had anomalous venous return, the pulmonary veins emptying into the right atrium; another had malrotation of the conus arteriosus; and still another had a large defect of the interatrial septum in the area of the foramen ovale. Another case listed as defect of the interventricular septum bore a relation to the Eisenmenger complex: in addition to the septal defect there was dextroposition of the aorta, hypertrophy of the right ventricle, a bicuspid aortic valve, a single coronary-artery orifice and a persistent ostium secundum. The 1965-gm. female infant survived delivery for twenty-one hours, dying with cyanosis and respiratory failure; the heart weighed 14 gm. and was not enlarged. In all these cases the defect of the interventricular septum was large, and presumably there was abundant mixing of oxygenated and unoxygenated blood. Functionally, these cases more closely resembled the cor triloculare univentriculare than the typical pattern of septal defect found in the older age group in which the defect is usually small and located at or just below the membranous portion of the interventricular septum.

By way of contrast, the 6 cases of defect of the interatrial septum were not associated with cardiac anomalies elsewhere, except in the last 2 cases above. The hearts in this group were usually quite small, the largest weighing 22 gm. In 1 case there was congenital absence of the gall bladder; in another there was microcephaly and multiple anomalies of the central nervous system.

Clinical Diagnosis

It is extremely difficult to predict the type of congenital cardiac malformation that will be found at autopsy. The clinical features of these cases were monotonously uniform, and there were few points that could help a clinician decide which of a variety of possible malformations a given infant might have. Cyanosis and respiratory difficulty developing at or shortly after birth were present in all patients who were not stillborn. The most intense degrees of cyanosis were observed in the cases with complete transposition of the great vessels without intracardiac shunts. Often, this cyanosis was not modified when the infant was placed in oxygen. Less constant degrees of cyanosis were observed in infants with tetralogy of Fallot or defect of the interatrial septum. As might have been expected cyanosis was not present in the 2 infants with bicuspid aortic valves nor in the infant with almost complete stenosis of the aortic valve due to endocardial sclerosis. Nor was cyanosis so prominent in infants with coarctation of the aorta until cardiac failure developed.

Murmurs were noted in 13 per cent of the cases; they were not heard in other cases with similar lesions. However, murmurs of the nature described in the clinical records are frequently heard in infants who prove to be free from cardiac malformations.

Cardiomegaly — increase in heart weight in relation to body weight — was almost always found at autopsy. Sometimes, it appeared profitable to distinguish between cardiomegaly that was present at birth and cardiomegaly that developed and increased after birth. Presumably, in the latter group, cardiomegaly represents work hypertrophy in an effort to cope with an abnormal post-natal circulation, whereas in the former group the cardiomegaly may be either an intrinsic component of the malformation (as in cases of idiopathic hypertrophy) or a response to an abnormal fetal circulation that imposed added work upon the heart — for example, valvular lesions. However, the mechanism whereby specific malformations may produce cardiomegaly at birth by increasing work loads during fetal life is not readily apparent from analysis of these cases. In the cases of large defects of the interventricular septum and cor triloculare and cor biloculare, the heart was usually enlarged to percussion at the initial physical examination made shortly after birth. By contrast, in cases in which transposition of the great vessels dominated the anatomic findings, the heart was not conspicuously enlarged at birth but increased rapidly in size, becoming proportionately larger as the infant continued to survive. Cardiomegaly was not usually prominent at or shortly after birth in the cases of coarctation of the aorta, tetralogy of Fallot or endocardial sclerosis; however, cardiomegaly was observed in most of these cases at autopsy, although to a lesser degree than in the cases of transposition or ventricular defect.

Electrocardiography did not appear useful as a diagnostic aid during the neonatal period. It was used only in a few of the more recent cases, but the tracings merely showed bizarre patterns that were not specifically diagnostic. However, the potential value of electrocardiography as a diagnostic tool in cardiac disease of the newborn is not accurately assessed by the few random and incomplete tracings found in the records of these cases.

In the following case a correct anatomic diagnosis was made before birth.*

*Reported through the courtesy of Dr. Arthur W. Tucker, Jr.

A 28-year-old gravida 2, para 0, who had an uneventful prenatal course, went into labor after rupture of the membranes at 43 weeks' gestation. After 5 hours of normal labor a male infant was delivered. The fetal heart beat had been heard at a constant rate of 60 per minute during the patient's office visits and during labor. After birth the infant's heart rate dropped to 30 per minute. Adequate respiration could not be established, and the heart became irregular before the infant died at the age of 1 hour. The heart rate was interpreted as an idioventricular rhythm, and a diagnosis of defect of the interventricular septum, with interruption of the conduction system, was made. Autopsy disclosed a 3150-gm. male infant. The heart weighed 50 gm. and was essentially bilocular. There was no septum in the atrium or in the ventricle. The segments of myocardium identified as left atrium and left ventricle appeared rudimentary, but their anatomic boundaries were not clearly defined. In addition, multiple accessory spleens were found in the splenic pedicle and lienorenal ligament.

Summary and Conclusions

Survey of 100 autopsied cases of newborn infants dying of congenital cardiac malformation representing more than 100,000 live births indicates that the most frequent cardiac malformations causing death within the first month of life are transpositions of the arterial trunks and large defects of the interventricular septum. The latter may be complete (classified as cor biloculare or cor triloculare) or incomplete (classified as septal defect). These observations contrast with the low prevalence of tetralogy of Fallot and patent ductus arteriosus as a cause of death during the first month of life, although these are the most common varieties of congenital heart disease encountered both in clinical practice and at autopsy.

We are indebted to Drs. Alexander S. Nadas and Clement A. Smith for helpful advice.

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ACUTE DISSEMINATED ENCEPHALOMYELITIS TREATED WITH ACTH*

Report of a Case

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RECENTLY, several encouraging reports have appeared concerning the use of ACTH and cortisone in isolated cases of acute disseminated encephalomyelitis of noninfectious etiology.[1,6] We have had the opportunity to observe the course of a patient with this syndrome who was treated with ACTH. This communication reviews some current concepts regarding encephalomyelitis and presents a case illustrating an apparently favorable response to ACTH therapy.

Case Report

E.G. (M. 44074), a 22-year-old single graduate nurse, entered the Beth Israel Hospital in the evening of August 16, 1953, complaining of pain in the back, weakness of the legs and difficulty in urination. Three days previously she had noted backache and paresthesias across the hips. The backache became more severe. One day before admission her neck became stiff, and her legs weak. She stated that on the day of admission she was unable to "empty her bladder completely." None of the other symptoms had receded. A review of the systems was noncontributory. The last upper respiratory infection had occurred 1 month before admission. She had received no recent immunizations. She had had convergence weakness of the left eye 1½ years previously, attributed to muscle imbalance by an ophthalmologist and improving after 2 months of muscle-training exercise. The past and family histories were otherwise noncontributory.

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Physical examination showed a mildly ill, well developed woman in some distress because of backache. There was slight redness of the pharynx. Respiratory motions were good.

The temperature was 99°F. by mouth, the pulse 96, and the respirations 20. The blood pressure was 160/65.

On neurologic examination Kernig's sign was present. The pupils reacted well, and the optic disks were normal. The 2d to 12th cranial nerves were normal. There was no motor weakness of the trunk or extremities. The left biceps, triceps and periosteoradial reflexes were moderately hyperactive whereas the right were normal. Abdominal reflexes were normal. Knee and ankle jerks were markedly hyperactive bilaterally. Heel-to-knee and finger-to-nose tests were accurately performed. Light touch was felt as paresthesia over the buttocks, and pinprick was not perceived over the back at the level of the 1st lumbar segment. Both were normal elsewhere.

After admission the patient was catheterized owing to inability to void, and 250 cc. of urine was obtained. Lumbar puncture revealed clear cerebrospinal fluid under an initial pressure equivalent to 145 mm. of water and containing 20 mononuclear cells per cubic millimeter and 72 mg. of protein per 100 cc. The gold-sol curve was 1111000000. Culture for fungi was negative, as was a blood Hinton test. The hemoglobin was 13.9 gm. per 100 cc., and the white-cell count 10,300, with 71 per cent neutrophils, 27 per cent monocytes and 1 per cent basophils. The urine was normal. Serum heterophil-antibody agglutination was negative. Roentgenograms showed the heart, lungs and cervical, dorsal and lumbar spine to be within normal limits.

During the first 2 days in the hospital the illness progressed with alarming rapidity. Twenty-four hours after admission gross weakness had developed in the legs. Constant urinary drainage was initiated owing to inability to void. The temperature rose to 102.4°F.; the patient became restless and confused and vomited once. Weakness developed in the arms. Thirty-six hours after admission the legs became almost completely paralyzed, and touch perception disappeared below the hips. At this time the spinal fluid con-

tained 300 fresh red cells and 420 white per cubic millimeter, of which 16 per cent were polymorphonuclear leukocytes and 84 per cent lymphocytes, with a protein of 218 mg., glucose of 75 mg. per 100 cc. and chloride of 120 milliequiv. per liter of chloride. The Hinton test was negative.

The patient was seen by a neurologic consultant approximately 48 hours after admission. During questioning she tended to fall asleep. He found her restless and irritable, but with normal mental function. There was unsustained, fine nystagmus on looking up or to either side. A slight blurring of the optic disks was of doubtful significance. Visual acuity and fields were normal. The facial muscles contracted well. Hearing was acute. There was marked nuchal rigidity. The arms were slightly weak, though reflexes were present and equal, and no sensory defect was noted. The intercostal muscles contracted well. The abdominal muscles were weak, and abdominal reflexes were absent. The legs were extremely weak, and tendon reflexes were diminished. The plantar reflexes were extensor. Stroking of the foot produced more vigorous flexion at hip and knee than was possible voluntarily. There was loss of pain perception up to the thoracic margin, and impairment of touch perception in the thighs and lower legs. Position sense of the toes was faulty though vibration sense was retained. Hamstring spasm was present. It was concluded that the patient had signs pointing to involvement of the corticospinal tracts bilaterally in either the upper thoracic or the cervical cord or both, of the lateral spinothalamic tracts about the level of the 8th thoracic dermatome and of the posterior columns. In addition there was evidence of meningeal irritation. The diagnostic impression of the neurologist was that of an acute, demyelinating disease involving the brain stem and spinal cord.

Forty-eight hours after admission, on the basis of the critical appearance of the patient, the deteriorating course and the extremely shallow respirations, it was decided to administer ACTH. Accordingly, 25 units was given intramuscularly every 6 hours. She also received a low-salt diet and potassium chloride by mouth. Aqueous penicillin, 300,000 units, and streptomycin, 0.5 gm. twice daily, were given as prophylaxis against urinary-tract infection. She was observed frequently throughout the next 24 hours. Six and a half hours after the first dose of ACTH she awoke from sleep with the first signs of improvement. She was more alert, and breathing was stronger. During the next morning, fifteen hours after the initiation of therapy and after 75 units of ACTH, there was further improvement in sensorium and respirations. Her arms were stronger; she could now move her toes, and the plantar reflexes were flexor. The temperature had dropped to 99.4°F. by rectum.

Twenty-four hours after the onset of therapy nuchal rigidity lessened, and by 36 hours the neck was almost fully supple. Arm strength was almost normal, and she could lift her knees off the bed. Forty-eight hours after the onset of therapy pruritus of the arms, chest and shoulders, in the areas of paresthesias before therapy, was a bitter complaint. Streptomycin was discontinued, and sulfisomidine (Elkosin), 4 gm. daily, administered. Three and a half days after the onset of therapy cutaneous pain sensation was entirely normal. On the 4th day pruritus began to diminish. On the 5th day of therapy the dosage of ACTH was reduced to 80 units daily. At the end of a week she could stand with assistance and was receiving physiotherapy. On the 9th day dosage was further reduced to 60 units daily. By the end of 2 weeks she had her 1st voluntary bowel movement. On the 16th day of therapy dosage was reduced to 45 units of ACTH a day. Within 2 days subjective numbness of the left arm, hand and of the abdomen had returned, and paresthesias, which had receded to the hips, rose to the level of the subcostal margin. Though careful examination failed to reveal objective changes, the dosage of ACTH was increased to 80 units daily, and 4 days later the paresthesias had again receded and the numbness disappeared. Starting on the 24th day of therapy, daily dosage of the hormone was gradually reduced without incident. ACTH was omitted on the 44th day of therapy.

Fifty-five days after the start of therapy and 10 days after its completion the patient was discharged fully ambulatory. Two weeks later the indwelling catheter was removed. Eight months after discharge she was working full time. She noted easy fatigue of her leg muscles on climbing stairs and required manual pressure on the abdomen to complete bladder emptying. Otherwise, she felt well. Examination at this time revealed only hyperactivity of knee and ankle jerks and absence of the left upper abdominal reflex. Table 1 presents a summary of events.

TABLE 1. *Summary of Neurologic Findings.*

Day of Illness	Total Dosage of ACTH	Nuchal Rigidity	Clouding of Sensorium	Nystagmus	Impairment of Proprioception	Loss of Sensation to Light Touch	Leg Weakness	Bladder Impairment
	mg.							
4*		+	0	?	0	±	0	++
6		++++	++	++	++	++	+++	+++
7†	100	++	0	?	?	++	++ to +++	+++
8	200	±		+	0	+ to ++	++	+++
10	400	0		0		+	++	+++
20	1195					+	+	+++
47‡	2785					±	±	++
(10th month after illness)						0	0	±

*Day of admission.
†Beginning of therapy.
‡Cessation of therapy.

Discussion

Acute disseminated encephalomyelitis is characterized by the rapid onset of symptoms and signs of disseminated damage to the white matter of the central nervous system. It often follows the exanthemas (postinfectious encephalitis), and vaccinations (postvaccinal encephalitis), but may occur without recognizable antecedent. Stupor, ascending paralysis, cerebellar and cranial-nerve signs, sensory disturbances, sphincter dysfunction and many other central-nervous-system manifestations appear in rapid progression and various combinations. Though the course is usually self-limited, death or permanent sequelae occasionally ensue. In contrast to multiple sclerosis there is little tendency for recurrence. The underlying histologic lesion consists of multiple foci

TABLE 2. *Effect of ACTH in Reported Cases of Encephalomyelitis.*

SOURCE	CASE NO.	AGE	SEX	ONSET OF SYMPTOMS	DURATION OF NEUROLOGIC SYMPTOMS BEFORE TREATMENT	DAILY TREATMENT	RESULTS	EVALUATION*
Miller[1]	1	22	M	5th day after upper respiratory infection	42 hr.	30 units of ACTH for 2 days; 40 units for 3 days.	Improvement within 90 min. of booster; patient well in 10 days (see text).	Benefit
	3	31	M	Day after chilling	12 days	80 units of ACTH for 2 days; 100 units of penicillin for 5 days.	Improvement in 12 hr.; mild spastic paraplegia 3 mo. later.	Benefit
Miller & Gibbons[2]	1	11	M	6 wk. after upper respiratory infection associated with rheumatic manifestations	36 hr.	125 units of ACTH for 1 day; 25 units for 1 day.	Improvement in 12 hr.; patient well in 3 days.	Benefit
	2	2	M	4th day of measles	4 days	100 units of ACTH for 5 days	Improvement in 12 hr.; at 3 wk. patient emotionally labile; 100 per cent recovery eventually.	Benefit
Miller & Gibbons[3]	1†	14	M	5th episode on 4th day of upper respiratory infection	12 hr.	100 units of ACTH for 1 day	Improvement in 6 hr.; patient well in 7 days.	Benefit
				6th episode on 4th day of upper respiratory infection	"Immediate" treatment	ACTH (? dose)	Improvement in 12 hr.; patient well in 3 days.	Benefit
	2‡	12	M	1st episode on 9th day of upper respiratory infection	15 hr.	125 units of ACTH for 1 day; 100 units for 2 days.	Improvement in 12 hr.; patient well in 4 days.	Benefit
				4th episode on 3d day of upper respiratory infection	1 day	525 units of ACTH in 5 days; penicillin.	Improvement in 12 hr.; patient well in 7 days.	Benefit
	3§	13	F	2d episode on 3d day of upper respiratory infection	8 days	ACTH (? dose) for 5 days	Improvement in 12 hr.; patient well in 5 days.	Benefit
Garrison[4]		22	M	12th day after rabies vaccine	1 day	300 mg. of cortisone for 2 days; 100 mg. for 4 days.	Improvement in 24 hr.; patient almost well on 4th day; 5 wk. later positive Babinski sign remained.	Benefit
Ligterink[5]	B	21	M	10th day after smallpox vaccination	? (few hours)	100 units of ACTH for 1 day; 80 units for 1 day; 60 units for 1 day; treatment stopped after 6th day.	"Immediate" response; fever & paresis gone in 24 hr.; patient well in 5 days.	Benefit
	C	60	M	9th day after smallpox vaccination	12 hr.	50 units of ACTH for 12 hr.; 100 units for 1 day; 75 units for 2 days; 50 units for 1 day.	Patient mentally clear & neurologic signs gone in 24 hr.	Benefit
U.S. Armed Forces[6]			¶	After smallpox vaccination	?	ACTH (? dose)	Patients "appear to have been benefitted"	
Miller[3]	2	6	F	6th day of chicken pox	5 days	25 units of ACTH for 3 days; 50 units for 1 day; penicillin.	Improvement in 3 days; patient almost well in 5 days.	No benefit
	4	6	M	6th day of chicken pox	48 hr.	100 units of ACTH for 3 days	Very slight improvement in 24 hr.; great improvement in 48 hr.; patient well in 6 days.	No benefit
	6	30	F	No prodrome	19 days	80 units of ACTH for 6 days; 40 units for 2 days; none for 1 day; 100 units for 5 days; 75 units as booster for 1 day (at ? time).	Continued progression	No benefit
Miller & Gibbons[3]	3	3½	F	6th day of measles	2 days	100 units of ACTH for 1 day; 50 units for ½ day; patient died.	Death on 2d day of treatment	No benefit
Ligterink[5]	A	2	M	During measles	?	75 units of ACTH for 1 day; 50 units for 1 day; gradual drop to 10 units on 11th day; then treatment stopped.	"Striking improvement" apparently beginning in 3 days; patient well in 6 days.	No benefit

*Made by present authors.
†6 episodes.
‡4 episodes.
§2 episodes.
¶"Small number"

of mononuclear-cell infiltration in the Virchow–Robin spaces about venules and small veins, with demyelination and microglial proliferation in the surrounding parenchyma. The axons in these areas are relatively, but not completely, undamaged.

Encephalomyelitis is well known to reverse from a progressively downhill course and to improve rapidly. Thus, in any case, evaluation of the effectiveness of therapy is difficult. The prompt reversal of progressive disease on institution of ACTH therapy, with relapse on reduction and remission again with increase in the dosage, strongly suggests a therapeutic response. In view of the known rapidity of action of the hormone on acute inflammatory processes and the prompt response in 10 of 15 recorded cases (discussed below) we believe that improvement within twenty-four hours is a useful criterion of ACTH effectiveness in this syndrome.

Favorable Cases

Miller[1] and Miller and Gibbons[2,3] have reported the treatment with ACTH of 13 episodes of encephalomyelitis occurring in 11 patients (Table 2). Utilizing the criterion of improvement beginning within twenty-four hours as due to ACTH, we considered 9 of these episodes (in 7 patients) to have been favorably influenced. The first patient listed received only 10 units of ACTH per day by subcutaneous drip. Remission began promptly when a 20-unit intramuscular booster dose was added later the first day. After a relapse 20 units of ACTH was given intramuscularly on the second day, initiating prompt remission that progressed until the patient was well. The next patient whose illness was favorably influenced had a spastic paraplegia three months later. Two more were free of residua. Five other favorable episodes occurred in 3 siblings with familial recurrent encephalomyelitis. These 5 episodes lasted an average of six days, whereas 7 other episodes in the same patients, untreated because they were milder, lasted an average of ten days. Miller and Gibbons[3] regard this difference in duration as suggestive evidence of a therapeutic effect of ACTH. Garrison[4] described improvement of a patient within twenty-four hours of the beginning of cortisone therapy. Ligterink[5] reported 3 cases of encephalomyelitis in 2 of which 100 units of ACTH was given on the first day, with a response "immediately" and within twenty-four hours, respectively. A few cases of encephalitis apparently responsive to ACTH were reported in the *United States Armed Forces Medical Journal*. However, no details are given.[6] We believe that the case presented above, with its prompt improvement and reversal of a mild relapse by ACTH, belongs in this "benefited" group.

Unfavorable Cases

In 2 of Miller's[1] patients, given 25 and 100 units of ACTH on the first day, significant improvement did not begin until forty-eight and seventy-two hours, respectively, after the onset of therapy. In 2 other patients described by Miller[1] and by Miller and Gibbons,[2] with initial daily doses of 80 and 100 units of ACTH, there was no improvement. In Ligterink's[5] unfavorable case, in spite of an initial dose of 75 units on the first day, improvement did not begin until three days after the start of therapy.

Rationale of Therapy

Increasing experimental and clinical evidence of the allergic nature of encephalomyelitis provide a basis for the use of adrenal steroids and ACTH. Experimental encephalomyelitis histologically similar to the human form may be induced by single or multiple "sensitizing" subcutaneous injections of brain, spinal-cord or nerve emulsions into rabbits, monkeys, guinea pigs and other animals.[7] Further evidence that this experimental syndrome is an allergic process lies in the findings that positive skin tests may be present against the injected brain as antigen,[8] that the experimental syndrome may be inhibited by agents known to inhibit the development of hypersensitivity (pyromen, salicylates, para-aminobenzoic acid, nitrogen mustard, cortisone and ACTH[7,9,10-12]) and that the syndrome is accentuated by the use of the adjuvant of Freund et al.[8] injected with the nervous tissue. Evidence that clinical encephalomyelitis may be a syndrome of hypersensitivity consists of a suitable interval after the inciting disease or injection (presumably the time necessary for development of hypersensitivity), an almost invariably fruitless search for infectious agents and occurrence of some cases of encephalomyelitis in association with well known manifestations of hypersensitivity. Csermely[13] reported encephalomyelitis in association with urticaria after antitetanus injection. Pickar and Kramer[14] described an episode of encephalomyelitis that followed antirabic therapy in which there was fever, erythema and swelling at the sites of inoculations. After recovery the patient was sensitive to Semple vaccine by skin test.

Summary and Conclusions

Fifteen patients with 17 episodes of acute disseminated encephalomyelitis treated with ACTH or cortisone have been described in the recent literature. Improvement appeared promptly in 10 patients with 12 episodes.

An additional case, arising without known inciting disease or vaccination, in which treatment with ACTH was followed by a prompt remission of symptoms, is presented. A mild relapse followed reduction in ACTH dosage and was reversed by another increase in the dose. Ten months after onset, mild weakness of the legs and some difficulty in urination remained.

Both clinical and experimental evidence suggest that encephalomyelitis sometimes arises on a basis of

hypersensitivity. Because ACTH and adrenal steroids are often useful agents in such disorders, further trial of these principles in the treatment of acute encephalomyelitis appears warranted.

We are indebted to Dr. Raymond D. Adams, chief of the Neurology Service at the Massachusetts General Hospital, and Bullard Professor of Neuropathology at Harvard Medical School, for permission to report his findings in this case.

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MEDICAL PROGRESS

CARDIAC DISEASE IN PREGNANCY

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IN considering the problem of cardiac disease in pregnancy one must have a reasonable knowledge of the physiologic changes that appear in the pulmonocardiovascular systems during normal pregnancy. Much investigation has been done in this field. Although there are differences of opinion about the exact physiologic findings, certain definite concepts are becoming generally accepted. In this paper an attempt is made to state these concepts, although one must realize that they are not, as yet, scientific facts.

The reports of various clinics throughout the country show the incidence of organic heart disease in pregnancy to vary from 0.3 per cent to 2 per cent. The lower percentages are reported from clinics in several sections of the country where rheumatic fever is somewhat less frequent. It is generally accepted that rheumatic heart disease constitutes from 85 per cent to 95 per cent of the cases of organic heart disease in pregnancy, and the majority of these are mitral stenosis. In the presence of symptoms and signs suggesting organic heart disease, it is unimportant whether or not there is a positive history of rheumatic fever. It has been reported that as many as half the patients with definite rheumatic heart disease do not give a clear history of previous rheumatic infection.

Congenital heart disease accounts for 1.5 per cent to 2.5 per cent of the cases of cardiac disease in pregnancy. In view of the present-day approach to the repair of congenital lesions through surgery, it is important not only to classify the lesions as congenital but also to determine as accurately as possible the nature of the anomaly present. History and physical examination are often very inadequate. Careful fluoroscopic examinations, venous catheterization, contrast mediums and other studies may be necessary.

Half the cases of dissecting aortic aneurysm reported in women under forty have occurred during pregnancy. Many of these cases have revealed medial necrosis of the aorta.

An increased tendency to the development of paroxysmal atrial tachycardia of functional origin has been noted in normal pregnancy.

At present there is an average death rate of between 2 per cent and 3 per cent in cases of heart disease in pregnancy. According to Ullery[1] congestive heart failure is the most common cause of death in pregnancy. On the other hand Wallace and her co-workers[2] report that in New York City postpartum hemorrhage exceeded infection and cardiovascular disease as the leading cause of maternal death. Hamilton and Thomson[3] note that the principal causes of death among their fatal cases of cardiac disease were congestive heart failure, 56.1 per cent, sepsis, 14.6 per cent, pulmonary embolism, 12.2 per cent, shock hemorrhage, 4.9 per cent, toxemia of pregnancy, 4.9 per cent, bacterial endocarditis, 4.9 per cent, and toxic hepatitis, 2.4 per cent. These authors report that 25 per cent of all cardiac deaths occur in the long months of pregnancy before delivery, and 75 per cent in the brief period of the puerperium. If the patient has not had heart failure before term the maternal mortality post

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partum is low, scarcely 2 per cent. If a patient has had congestive heart failure before term, and has been cured, the mortality is 8 per cent. If congestive heart failure is actually present at delivery the mortality rate is 45 per cent.

Hamilton[4] states that many who emphasize the role of rheumatic fever in determining the entire life course of adults with rheumatic heart disease believe that smoldering rheumatic fever is an important factor in the prognosis of pregnancy. The general belief is that pregnancy has little influence in activating rheumatic fever. Although some believe that active rheumatic fever is a fatal complication in pregnancy, many do not agree with this opinion.

Physiologic Changes in Normal Pregnancy

Hamilton[4] describes an abrupt fall in vital capacity, reported to average 250 cc. immediately, after delivery consequent to suddenly decreased intra-abdominal pressure. Cugell and his associates[5] find slight increases and slight decreases in the vital capacity during pregnancy, with no significant trend. They state that the most striking alteration noted in their respiratory studies is a marked increase in ventilation at rest, which can be detected as early as the first trimester and amounts to 42 per cent at term. The oxygen requirement increases later, and the increment is never as large as that of ventilation. They further note that hyperpnea occurring early in pregnancy is not due to "voluntary" hyperventilation, but suggest that it is due to the response of an increasingly irritable respiratory center. This may explain the early appearance of dyspnea, usually during the second to the fifth month, and may also explain the unusual complaint of dyspnea at rest without dyspnea during exercise. These authors find that the average basal metabolic rate in the nonpregnant woman is 4 per cent and increases to 18 per cent at term. They are of the opinion that the latter value has little meaning because the fetal surface and metabolism were not considered in the calculation.

Pregnancy is accompanied by an increase in oxygen consumption from about 15 per cent to 25 per cent above normal, and the uterus, with its contents, accounts for the greatest part of this increase. The arteriovenous oxygen ratio is higher than that in the nonpregnant state. Actually, the observed increases are greater than the increase in metabolism.

Studies on cardiac output in pregnancy show differences in opinion that at times appear marked. It is probable that the correct answers lie somewhere between the extremes. Reynolds[6] states that there is a 30 per cent increase in cardiac output as pregnancy advances, with a return to nonpregnant levels a few weeks after parturition. Somewhat higher levels are noted by Hamilton and Thomson,[3] who report a rise in output beginning about twelve weeks or earlier, increasing slowly at first but then quite rapidly from the sixth through the ninth lunar month and reaching 50 per cent above normal at the point of maximal increase. During the tenth lunar month it diminishes definitely and may even approach the average nonpregnant level, and finally returns to normal in the second week post partum.

Adams,[7] employing the Fick principle and the Evans blue-dye-dilution technic, reports conclusions that vary somewhat from those of other investigators. He notes an increase in cardiac output toward the end of the first trimester, reaching a peak of 32 per cent at approximately twenty-eight weeks of gestation. His data indicate that as pregnancy progresses beyond this point there is a gradual decline in cardiac output, reaching nonpregnant levels or lower at thirty-eight to forty weeks of gestation. He emphasizes the importance of an increase in cardiac output from a level of 5.5 liters per minute at term to 7.1 liters per minute immediately after delivery — a rise increase of approximately 30 per cent. This increased output is maintained over the first few days post partum, reaching levels characteristic for nonpregnant patients by the end of the second postpartum week. This author describes two factors that account for this sudden increase in output after delivery. As the uterus contracts, the extra blood volume is squeezed from the maternal sinuses into the systemic circulation, and also the pressure of the uterus on the great veins of the pelvis and the lower extremities has been released. Both these factors result in an increase in venous return to the heart and, therefore, an increase in cardiac output.

Adams[7] states, as many others do, that the blood volume tends to parallel the plasma volume although the increase in the former during pregnancy is relatively less than that in the latter. He notes that there is an 11 per cent rise in blood volume at thirty-four weeks of gestation. Increase in plasma volume begins at about the end of the first trimester. This rise is gradual and does not reach a maximum until thirty-two to thirty-four weeks of gestation, an increase of approximately 22 per cent. Adams reports that there is no significant fall in plasma volume during the last trimester to correspond to the decrease in cardiac output. However, most students of this problem assume that there is a reduction in plasma volume during the last four weeks of pregnancy.

Caton et al.[8] use red blood cells tagged with radioactive iron in determining blood volume. They reach an average increase in red-cell volume of 40 per cent at term and an increase in plasma volume of 55 per cent sixty days before delivery. Berlin and his coworkers,[9] employing P^{32}-labeled red cells, report that because the fall in red-cell volume is greater than the rise in plasma volume in the first two months of pregnancy, there is a small drop in the whole-blood volume during this period. From their data they believe that a true anemia exists in the first and second trimesters.

It is commonly accepted that during pregnancy the rate of blood flow rises. Hamilton and Thomson[3]

report increases about the seventeenth week of gestation that remain until the thirty-sixth week, with a decrease just before term. Presumably, the accelerated blood flow is secondary to increased cardiac output and decreased blood viscosity. Reynolds[6] notes that pregnancy has an effect on the peripheral blood supply. During the first trimester of pregnancy there is no change in the circulation time of the extremities, but from the beginning of the second trimester to term the circulation rate rises progressively, reaching the upper limit of normally accepted values. The circulation in the uterus is maintained at no expense to the extremities, and it is achieved primarily by an increase in cardiac output.

A preliminary study by Burt[10] indicates a tendency to muscular and cutaneous vasodilatation in the later months of pregnancy.

The basal arterial blood pressure remains within normal limits during pregnancy, though there is a tendency for both the average systolic and diastolic pressures to diminish from the fourth to the ninth lunar month. There is, however, a disproportionate decrease between the systolic and diastolic blood pressures, resulting in an increase in the pulse pressure. Adams[7] states that the total peripheral resistance is reduced in pregnancy, largely, it is thought, as the result of decreased blood pressure. This pressure is reduced by the influence of the increased maternal sinuses and the arteriovenous shunt. The increased cardiac output, the decrease in blood viscosity due to hemodilution and the increased vascularity of the pelvic organs also tend to reduce the peripheral resistance. During the pains of labor both the systolic and the diastolic arterial pressures rise, as the venous pressure does.

The mechanical effect of supplying a large vascular bed, uterus and fetus, may be considerable; the blood vessels are numerous, large and tortuous. This situation has frequently been compared with arteriovenous fistulas in their physiologic effect. It has also been shown that, during the uterine contractions of normal labor, the arterial inflow to the placenta is greatly diminished. The blood contained in the placenta is squeezed out. These repeated small autotransfusions may cause transient rises of the venous pressure, thus producing infiltration of fluid from the capillaries so that total blood volume is gradually diminished during labor. No such gradual preparation for obliteration of the placental circulation is possible with abdominal delivery. This may explain in part the increased mortality rate associated with cesarean section in patients with cardiac disease.

The pregnant woman shows a marked tendency for salt and water retention. This may well be the initial step in the development of congestive heart failure. The changes in water balance and in blood volume, which may to some extent be controlled, are of great practical importance in the consideration of heart disease during pregnancy. The direct water-retaining and sodium-retaining effects of estrogens and progesterone appear to be in question. Their pituitary-stimulating effect apparently activates two chains of reaction. One is the increase of the antidiuretic hormone that is said to be present on occasion; the other, mediated by the ACTH of the anterior pituitary body, results in the liberation of salt-retaining corticosteroids in the adrenal cortex. The tendency to the retention of sodium and water is best corrected by a low-sodium intake and diuretics if necessary, rather than by attempts to change the endocrine pattern. Certainly, the prevention of sodium retention is one of the most important factors in the treatment of cardiac disease.

From the preceding physiologic studies it is evident that there are two critical periods during pregnancy and the puerperium when the cardiovascular system is placed under a severe strain; these are at approximately twenty-eight weeks of gestation and immediately post partum. However, a normal heart has no difficulty compensating for the increased work. White[11] associates increased work of the heart with increased output. Normally, the heart has sufficient reserve to meet the increased demands, but whether this happens in pregnancy or whether there is some hypertrophy to help assume the extra load has not been demonstrated. If any cardiac enlargement did occur it would be difficult to measure because of the changes in contour and position of the heart that usually take place during pregnancy. Reynolds[6] states that the load that pregnancy imposes on the heart is also suggested by the fact that as early as the fourth month of pregnancy both the longitudinal and transverse diameters of the heart increase perceptibly. However, as noted above, the significance of such changes is open to challenge at present.

There are numerous symptoms and signs due to the physiology of normal pregnancy that may be confused with the symptoms and signs of organic heart disease. Dyspnea and hyperventilation are common symptoms in the normal pregnant patient. Many women complain of palpitation, particularly at rest. There is considerable variation in the heart rate during pregnancy, with some tendency to acceleration and a return to normal shortly after delivery.

Loud systolic murmurs are common in pregnancy. They may often be confused with murmurs of aortic-valve disease, congenital lesions or organic mitral insufficiency. Although the majority of these murmurs are blowing in character many assume a harsh quality, and these are often greatly altered in intensity by inspiration and expiration. They are heard most frequently at the base of the heart and are often transmitted upward into the neck. Many are best heard at the apex, with transmission to the axilla or to the back. Some are heard precordially or substernally. It may often be impossible to evaluate these murmurs accurately until after delivery,

when most of them tend to disappear. No functional diastolic murmurs are present in normal pregnancy. A loud third heart sound is frequently heard. Accentuation of the second pulmonic sound is common during the third trimester, and it may be reduplicated.

Edema is a common problem in the normal pregnant woman.

X-ray and fluoroscopic examinations of the heart may be confusing. There may be little or no change in some women, and great changes in others. In the majority of cases there seems to be a tendency for an increase to occur in the area of the cardiac shadow in all its diameters; in others the increase may be limited to the region of the pulmonary conus. Correct interpretation of these changes is as yet not possible.

Vectocardiographic studies confirm the fairly common finding of a prominent Q wave in Lead 3 of the electrocardiogram. Horizontal positions of the heart in the electrocardiogram of normal pregnant women are noted by some; others, including this clinic, find only semivertical or intermediate positions. A shift in the mean electric axis to the left during the first two trimesters and a return to the right in the last trimester are repeatedly demonstrated.

In a study of heart disease in pregnant women it is of primary importance to have an understanding of the functional capacity of the patient's heart. This is necessary so that one may give thought to the significance of the patient's symptoms and signs and treat them intelligently. It is important to think in terms of functional capacity not only at the first meeting with the patient but also at each subsequent visit because the functional capacity of the heart may change at any time during the pregnant state, and this change may be a very abrupt and dramatic one. For purposes of common understanding it is best to use the classification of the heart established by the New York Heart Association:

Class 1. Patients with cardiac disease but without resulting limitation of physical activity. (Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.)

Class 2. Patients with cardiac disease resulting in slight limitation of physical activity. (They are comfortable at rest; ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.)

Class 3. Patients with cardiac disease resulting in marked limitation of physical activity. (They are comfortable at rest; less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.)

Class 4. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. (Symptoms of cardiac insufficiency or of anginal syndrome are present even at rest; if any physical activity is undertaken discomfort is increased.)

Undiagnosed manifestation. Patients with symptoms or signs referable to the heart but in whom a diagnosis of cardiac disease is uncertain should be classified tentatively in this group.

Evaluation of Cardiac Status in Pregnancy

Adams[7] is of the opinion that congestive heart failure occurs predominantly during the periods of increasing and maximal physiologic stress. The frequency of congestive heart failure has been seen to parallel closely the increases and decreases in cardiac output. A patient may experience decompensation for the first time during one of the two periods of maximal circulatory stress, at approximately twenty-eight weeks of gestation and immediately post partum. Heart failure during the first trimester may be expected to be intensified during the critical period. If the patient can be carried past the twenty-eighth week, in all probability her condition will improve during the last trimester. This author states that it is also true that if the pregnant patient with cardiac decompensation passes the twenty-eighth week safely, she may be expected to pass the immediate post-partum period with little or no difficulty. The conclusion is drawn that termination of pregnancy in patients during the last trimester because of cardiac decompensation is not physiologically sound. Hamilton[4] presents a somewhat different picture. He believes that it is unusual to encounter heart failure initially during or immediately after delivery if a patient has progressed safely during pregnancy. The average patient who is in congestive heart failure when delivered often becomes worse after delivery, even when delivery is precipitate and apparently effortless. This is undoubtedly due to the abrupt changes that follow the emptying of the uterus and the detachment of the placenta.

In the event of congestive heart failure after delivery for the first time, there is usually some severe complication to produce it — embolism, atelectasis of the lungs, surgical shock, toxemia, sepsis and sudden disorders of the heart beat, such as paroxysmal tachycardia, atrial fibrillation or atrial flutter.

Ullery[1] believes that several factors are to be considered in the total evaluation of the cardiac picture in the pregnant woman; they are the age of the patient, duration of the rheumatic state, frequency of the attacks of rheumatic fever, structural lesions of the heart, size of the heart, duration of the heart disease, presence of failure or a history of previous failure and the presence of concomitant disease. The course of pregnancy in the patient with cardiac disease is influenced more by these factors than by the actual number of previous pregnancies. It has not been possible to prove that repeated childbearing, in itself, has aggravated heart disease. It does not affect the pathologic processes, nor does preg-

nancy extend its influence on the heart much beyond the period during which the pregnancy is effective.

Finland[12] presents an optimistic point of view in a discussion of bacterial endocarditis. He states that remarkable success has been achieved in cases of subacute bacterial endocarditis complicating pregnancy and the puerperium. Treatment of the active infection during the course of pregnancy has proved as successful in the pregnant as in the nonpregnant patient. Proper and adequate therapy has resulted not only in the cure of the mother but also in the successful delivery of living and healthy children in the majority of cases. Properly managed, pregnant patients with cardiac disease in whom congestive heart failure and subacute bacterial endocarditis develop go through pregnancy very well.

Management of the Pregnant Patient with Heart Disease

Several general observations may be made concerning the care of cardiac patients during pregnancy. It is important that all patients be seen at least once weekly by both the obstetrician and the cardiologist. Patients whose condition is classified as "undiagnosed manifestation" should be treated as if they had definite signs of organic heart disease. In some cases it may not be possible to make a positive conclusion until after delivery.

Gorenberg and Chesley[13] recommend the following routine in relation to hospitalization of the cardiac patients: extra rest in the sixth, seventh and eighth months; weekly clinic visits for patients over twenty-five years of age; immediate hospitalization for all patients in Classes 3 and 4, with absolute bed rest until delivery; immediate hospitalization of all patients with a history of cardiac failure and absolute bed rest until after delivery; and immediate hospitalization at the first suspicion of decrease in cardiac reserve.

This program is much more conservative than that followed by most clinics. It is more or less generally accepted that patients in Class 1 should be admitted to the hospital at least a week before expected date of confinement and that they should be maintained on bed rest, and also that patients in Classes 3 and 4 should be admitted at least two weeks before term.

It must be impressed on all patients that they should communicate with the physician without delay if any unusual symptoms occur. All infections, regardless of nature or degree, must be considered seriously and treated promptly — even minor illnesses such as an upper respiratory infection may throw a patient with heart disease into congestive heart failure. If a diminution in vital capacity is noted at any period of pregnancy the onset of congestive heart failure must be suspected. It should be considered also if the pulse rate exceeds 110 per minute and the respiratory rate rises above twenty-four per minute.

Maintenance of proper nutrition of the patient is very important. Weight gain should be limited to 18 pounds. The diet must be carefully regulated, and the clinic patient should discuss her diet and possible changes with the nutritionist at each visit. A close watch must be kept on the patient's weight changes. A sudden increase proves the retention of fluid, with possible impending congestive heart failure. In such cases diuresis should immediately be effected under hospital conditions. All patients must be maintained on a low-sodium intake. Patients in all classes are restricted to diets containing not more than 1.5 gm. of sodium a day; those in Classes 2, 3 and 4 should be limited to a sodium intake closer to 1 gm. a day and further restricted to approximately 400 mg. during the period of the greater cardiac load, from the twenty-sixth to the thirty-fourth week. On admission to the hospital in preparation for delivery the patient should receive not more than 900 mg. of sodium a day. This restriction should be maintained until discharge from the hospital. Patients who have even minimal signs of congestive heart failure should be restricted to a diet containing not more than 200 mg. of sodium a day.

In recent years there has been much discussion in the literature concerning indications and contraindications for cardiac surgery in pregnancy. There are many favorable reports; there are also many authors who have adopted a more conservative approach to the problem. Some report that, since patients with tight mitral valves and severe pulmonary hypertension may have an attack of pulmonary edema, they should be considered candidates for mitral surgery without delay. Many patients have had mitral valvuloplasty for mitral stenosis and have gone through pregnancy successfully. This is true in cases in which surgery was done either before or during pregnancy.

Hamilton[4] is of the opinion that operation should be avoidable during pregnancy except in rare circumstances. Burwell[14] does not advocate mitral-valve surgery during the pregnant state. He believes that, with few exceptions, the patients who are in congestive heart failure can be brought to term and delivered normally with careful medical control. In his opinion the added stress of surgery can only increase the burden on an already overtaxed circulation. Furthermore, there is evidence that mitral-valve surgery frequently stirs up rheumatic activity, which is undesirable during pregnancy. He advocates mitral-valve surgery in these cases after the post-partum period. With this program, and the circulatory improvement that usually follows such surgery, there should be no need for sterilization. On the other hand, Ellis[15] is of the opinion that under certain circumstances it is proper to recommend mitral-valve surgery during pregnancy. If a woman with mitral stenosis had had progressive disability before her pregnancy to a degree sufficient for operation to have been advised at that time it is proper to recommend surgery during

the first four months of pregnancy since the risk of the operation at this time is less than if valvuloplasty were done later in pregnancy because of worsening of the cardiac state.

A moderate number of patients who have been successfully treated surgically for patent ductus arteriosus have done well later in pregnancy. This operation has also been successfully performed during pregnancy.

The uncommon case of hyperthyroid heart disease during pregnancy requires special consideration in the treatment of this condition. Except in the first few weeks of pregnancy the use of radioactive iodine is contraindicated because it destroys the fetal thyroid gland. Propylthiouracil is considered the drug of choice.

Congestive Heart Failure

If congestive heart failure occurs the pregnancy should be disregarded, and the failure treated vigorously. Digitalis is always indicated in the presence of congestive heart failure, however minimal. After the patient has been digitalized, whether during pregnancy or labor, it is advisable to continue the digitalis even though no further signs of failure are apparent. It should be continued through the puerperium. Digitalis should always be given in the presence of atrial fibrillation even though there is no evidence of congestive heart failure. When a history of previous atrial fibrillation is elicited it is important to digitalize the patient completely at any time during pregnancy even though the rhythm is normal at that time. Under full digitalization, if fibrillation occurs during the pregnancy or labor, the ventricular rate may be so well controlled that the cardiac output will remain adequate and serious consequences thus averted.

The immediate treatment of congestive heart failure in pregnancy is the usual treatment of failure under any other circumstances. Oxygen is nearly always indicated. Diuretics are often very helpful and should be used. There is no established evidence that there are any harmful effects of mercurial diuretics on the fetus. Oral administration of mercurial diuretics may be of much value in cases of chronic congestive heart failure.

On occasion, though not often, paroxysmal atrial tachycardia or atrial fibrillation may suddenly appear. In most cases it is desirable and important to stop the arrhythmia quickly; drugs such as quinidine or procaine amide may be used. Most authorities agree that these drugs are not oxytocic and may be given during pregnancy without fear.

Observation During Labor

Since the pulse, blood pressure and respiration serve as a reasonably reliable index of impending congestive heart failure it is important that these readings be checked frequently throughout labor, at least every half hour during the first stage and more frequently during the other phases, the possibility of the sudden onset of pulmonary edema being kept in mind. Particularly during the first few hours after delivery one must be constantly alert for such complications and prepared to treat with a minimum of delay any untoward symptoms.

Acute pulmonary edema may appear abruptly without previous warning and must be treated vigorously. Morphine or allied drugs should be given in adequate doses subcutaneously, and in extreme cases they may be given intravenously. Oxygen may be life saving and may be administered under positive pressure. Rapid venesection is very often of great value, and tourniquets on all four extremities may prove very effective. Antifoaming agents are occasionally useful in diminishing the pulmonary edema. Rapid digitalization is routinely indicated, and parenteral administration of diuretics is often of value. Whenever cardiac shock manifests itself it must be combated with pressor drugs such as Neo-Synephrine, Vasoxyn and Levophed. Aminophylline is often used in pulmonary edema though its effectiveness is questionable.

Fluids for parenteral administration must be given very cautiously during labor except as is urgently needed. If fluids are given intravenously during labor the rate must be slow, not over thirty drops a minute, and the minimal amount necessary should be given. Certainly, the use of any saline infusion is prohibited.

The patient should be well sedated during labor. Barbiturates and such drugs as morphine, Demerol, Dilaudid and Pantopon may be used. Scopolamine should be avoided lest it cause excitement.

There is some difference of opinion about the choice of anesthesia. Open-drop ether is an old and established form of anesthesia; low spinal and saddle block constitute the anesthetic of choice in many clinics. Pudendal block has been described by many as the safest procedure. However, it is the considered opinion of most that the problem concerning the type of anesthesia to be used should be resolved in the selection of a competent anesthesiologist, in whose hands the choice lies.

Delivery

The patient should be examined frequently during the first stage of labor to determine the onset of the second stage and full dilatation of the cervix as soon as possible after it occurs. She should be delivered then with as little delay as possible if the presenting part is well down in the pelvis. This prevents undue stress and strain. The cardiac patient should receive as much assistance in the second stage as possible. This stage should be terminated by forceps as soon as this becomes a safe and simple procedure. Difficult forceps delivery should be avoided at all cost.

It is generally agreed that cesarean section is contraindicated in the cardiac patient. Unless there is an absolute obstetric indication this procedure should not be performed. Hamilton and Thomson,[3] in arguing against cesarean section, stated that their death rate was four times greater in abdominal delivery than when patients were delivered normally.

Third Stage of Labor

The end of the second stage of labor and the period throughout the third stage may usher in the rapid onset of congestive heart failure. It may be advantageous to use tourniquets on all extremities at the end of the second stage in all patients who are in failure at the time; there may be value in their use at this time in the patient with a history of previous failure. Even though the number of patients who go into failure for the first time during labor is small it may be worth while to use tourniquets routinely at the end of the second stage.

Oxytocics should not be given routinely during the second stage. Ullery,[1] like others, believes that such drugs increase the contractability of the uterus and, by forcing greater amounts of blood than usual from the maternal sinuses into the blood stream, may increase the hazard of congestive heart failure in the third stage. However, in post-partum atony, the use of a dilute solution of Pitocin intravenously may be necessary. The loss of a moderate amount of blood in the third stage may be helpful, acting in the nature of a venesection. However, this must be carefully watched, for excessive blood loss may be extremely dangerous to the cardiac patient.

At delivery and in the early puerperium some form of prophylactic therapy against bacterial endocarditis is generally advocated for patients with rheumatic and congenital heart disease. How long this treatment should be continued has not been sufficiently studied. It is common practice to give procaine penicillin in doses of 600,000 units intramuscularly at the onset of labor, and thereafter 300,000 units twice daily for at least five days post partum. Finland[16] has suggested the use of a rapid-acting penicillin rather than procaine penicillin, to be administered in doses of 200,000 to 300,000 units intramuscularly at the start of delivery and continued every three hours for two or three days. There is as yet no careful study or well controlled series to demonstrate the effectiveness of prophylaxis as commonly practiced today in the prevention of bacterial endocarditis after delivery.

Post-Partum Care

Lactation should be permitted except in the presence of congestive heart failure. Patients in Classes 3 and 4 should have their activities restricted and should be kept in the hospital for approximately two weeks post partum. Patients who are in congestive heart failure should remain in the hospital until improved. All patients should be advised to limit their activities carefully for at least another month after discharge from the hospital.

Conclusions

A proper understanding of the physiologic changes that take place in normal pregnancy and in pregnant patients with cardiac disease leads to a more intelligent handling of the problem of heart disease in pregnancy. The present-day approach to this problem is primarily proper treatment of the heart disease and noninterference with the pregnancy. Under proper treatment the patient should be carried through pregnancy and allowed to deliver normally. The cardiac status should be treated as though the patient were not pregnant and the obstetric problem as though she did not have heart disease. Failure to make a proper diagnosis and to evaluate cardiac status may threaten the life of the patient. Hospitalization at the first sign of decompensation and continued hospitalization until well after delivery are essential. Patients in Classes 3 and 4 should have complete bed rest for the last few weeks of pregnancy. Proper rest and sufficient hospitalization for all classes in the post-partum period are extremely important. Most authorities agree that interference with pregnancy during advanced failure can result disastrously.

In mitral stenosis one may resort to valvuloplasty, but this surgical approach should be avoided during the pregnant state unless it appears necessary to save life. If mitral-valve surgery is performed the patient may undertake future pregnancies with much less fear of cardiac disasters.

Frequent observation of the patient during labor and delivery and in the post-partum period is most essential. Treatment of cardiac emergencies with a minimum of delay may make the difference between life and death. Vigorous treatment of pulmonary edema must be pushed. Fluid administration in the presence of heart disease should be slow and in minimal amounts during pregnancy and delivery. It is common practice to sedate patients well during labor with barbiturates and opiates. Some clinics prefer inhalation anesthesia, and many others regional types of anesthesia. It is believed, however, that the choice of a trained anesthesiologist is more important than the method employed. Cesarean section is to be performed only for obstetric reasons. The use of oxytocics in the third stage of labor should be avoided unless necessary for uterine atony.

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MEDICAL INTELLIGENCE

INTERFERENCE WITH UPTAKE OF RADIOIODINE TRACER DURING THE ADMINISTRATION OF VITAMIN-MINERAL MIXTURES*

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IN an attempt to explain the occasional discrepantly low value of radioiodine uptake found in tracer studies, it seemed that some of the vitamin-mineral preparations containing iodine might be involved. The interference of previously administered mineral or organic iodine with this test is well established, and after some organic iodine compounds, such as gall-bladder dyes, have been taken, the effect may be of long duration. The minimal blocking dose of iodine has not been established, but it may be quite small, since it is known that remissions in thyrotoxicosis can occasionally be induced by quantities of 1.5 mg. a day.[1] Elevation of protein-bound serum iodine levels and possible block of thyroid iodine uptake have been reported after the administration of Neo-Penil, an iodide salt of penicillin G.[2,3] There is iodine in the normal diet from seafood and iodized salt, among other sources. The level of this background intake probably varies widely, depending on personal habits, but if iodized salt is used at the table without restriction, it may be between 0.0004 and 0.0008 gm. of iodine per day. It may be noted that whereas the addition of sodium iodide to table salt was designed to prevent adolescent goiter, iodine-free salt is still available and, in some areas of Rochester, outsells the iodized product by two to one. Bread, which is assumed to supply about 2 gm. of salt to the normal diet (5 slices) is, much of it, in Rochester at least, made from noniodized salt.

At least 16 mineral-vitamin formulas commonly sold without prescription contain more or less iodine, and this might raise the total daily intake to a significant level in terms of blocking radioiodine uptake. To test this hypothesis 8 apparently euthyroid persons, none of whom had been taking vitamin-mineral supplements, were given daily two capsules of Gevral,§ a popular polyvitamin-mineral preparation that is stated to contain 0.5 mg. of iodine (as potassium iodide) per capsule (Table 1). This preparation was chosen because of its relatively high

TABLE 1. *Effect of Vitamin-Mineral Mixtures on Euthyroid Subjects.*

SUBJECT	UNIT NUMBER	AGE	UPTAKE BEFORE DRUG	PERIOD OF ADMINISTRATION	UPTAKE ON DRUG	UPTAKE AFTER DRUG
		yr.	%		%	%
R.B.	42603	40	33(12-20-54)	1-17-55 to 1-22-55 (5 days)	29(1-24-55)	
R.G.	238179	30	17(12-20-54)	1-17-55 to 1-22-55 (5 days)	14(1-24-55)	
F.G.	364343	30	42(12-20-54)	1-17-55 to 1-22-55 (5 days)	49(1-24-55)	
A.A.	383096	35	37(12-20-54)	1-17-55 to 1-22-55 (5 days)	13(1-24-55)	24 (2-7-55)
H.G.	382662	32	35(12-20-54)	1-17-55 to 1-22-55 (5 days)	24(1-24-55)	32 (2-7-55)
L.K.	9314	60	44(1-17-55)	1-18-55 to 1-25-55 (7 days)	28(1-25-55)	42 (2-7-55)
E.N.	201338	48	62(12-20-54)	1-17-55 to 1-26-55 (9 days)	16(1-26-55)	16.5(2-14-55; subject still on drug).
F.J.	252809	35	18(1-17-55)	1-17-55 to 1-23-55 (6 days)	30(1-25-55)	30 (2-14-55)

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§The stated content of a capsule of Gevral is as follows: vitamin A, 5000 *U.S.P.* units; vitamin D, 500 *U.S.P.* units; vitamin B_{12}, 1.0 microgm.; thiamine hydrochloride, 5.0 mg.; riboflavin, 5.0 mg.; niscinamide, 15.0 mg.; pyridoxine hydrochloride, 0.5 mg.; calcium pantothenate, 5.0 mg.; choline dihydrogen citrate, 100 mg.; inositol, 50 mg.; ascorbic acid, 50 mg.; vitamin E, 10 units; rutin, 25 mg.; purified intrinsic factor concentrate, 0.5 mg.; iron (as FeS O_4), 10 mg.; iodine (as KI) 0.5 mg.; calcium (as $CaHPO_4$), 145 mg.; phosphorus (as $CaHPO_4$), 145 mg.; Boron (as $Na_2B_4O_7 0.10\ H_2O$), 0.1 mg.; copper (as CuO), 1.0 mg.; fluorine (as CaF_2), 0.1 mg.; manganese (as MnO_2), 1.0 mg.; magnesium (as MgO), 1.0 mg.; potassium (as K_2SO_4), 5.0 mg.; and zinc (as ZnO), 0.5 mg.

iodine content although others may equal it. The I^{131} uptake of these subjects was measured before the test period, after five to nine days of drug and, in 4 cases, fourteen or more days after it was stopped. The technic used was that standard in this center: 60 microcuries of I^{131} standardized by the Isotope Center of the University of Rochester was given orally, and the radiation over the thyroid gland was determined in duplicate at twenty-four hours by means of a scintillation counter.

It is seen that the uptake was lowered very slightly in 2 subjects and increased slightly in 1. Three subjects appear to have been blocked, as judged by drops of 24, 11 and 16 per cent and significant rebound after the drug was stopped. One person had a sharp fall in uptake associated with marked increase in her sense of well-being, and is under study for possible hyperthyroidism. Another appears to have been blocked at the onset of the test and to have recovered; the cause of this block remains unknown.

This scattered response was not unexpected. Considering all the factors involved — iodine from food, differences in absorption from the bowel, and the considerable range of avidity of the normal thyroid for iodine — it is improbable that all people will react identically. The important fact is that some subjects were apparently blocked during the period of intake of the drug, and tended to recover their pretreatment level after stopping it. Although it is possible that some other component of the vitamin-mineral mixture is responsible for the effect observed, it seems more likely to be due to the iodine content.

Conclusions

The supplementary intake of iodine in vitamin-mineral preparations may interfere with diagnostic tests of radioiodine uptake. This may explain some of the unexpectedly low values found in any extended series of observations. It seems well to question candidates for determination of radioiodine uptake regarding their ingestion of compound vitamin-mineral preparations.

We are indebted to the six physicians who joined us as subjects in this experiment.

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THE BRITISH MEDICAL ASSOCIATION IN TORONTO

John W. P. Thompson, M.B.*

London, England

ONE of the unusual features of the joint annual meeting of the British, Canadian and Ontario medical associations at Toronto in June was the presence at several functions of the past-presidents, presidents and presidents-elect of all three associations, as well as a number of presidents of other organizations. This so baffled Sir Henry Dale, or so he pretended, that on the occasion of his being presented with the Medal of Honour of the Canadian Pharmaceutical Manufacturers' Association, he confessed that he was not sure to which of the "posse of presidents" he should particularly address his remarks. Needless to say he made no mistake, and all those present were delighted to see Sir Henry in such good form only a few days after the celebration of his eightieth birthday.

In actual fact the number of presidents was one less than it might have been, because Dr. Clarence Routley, who retired from the position of general secretary of the Canadian Medical Association last year, achieved the unusual distinction of being installed as the president of both the British and Canadian medical associations. No happier choice could have been made, for Dr. Routley's work for the Canadian Medical Association has been outstandingly successful and he has seen it grow into an influential organization that truly represents the medical men and women of Canada. A frequent and popular visitor at B.M.A. House in London, and at annual meetings of the American Medical Association, he has never taken a parochial view of medical affairs, and, as the *British Medical Journal* has said, it was not unexpected to find him "an active force in the formation of two important international medical organizations—the World Health Organization and the World Medical Association."

The joint annual meeting was the largest medical convention ever to be held in Canada, over 3000 Canadian doctors attending, as well as more than 370 members of the British Medical Association. There were in addition some visitors from the United States, including, to everyone's pleasure, the president of the American Medical Association. Many of the travelers from Great Britain overcame great difficulties in reaching Toronto, for the strike of stewards and deck hands on the British liners began just before the main party was due to set sail, and the air liners were booked to capacity. In the end only a few had to cancel the trip, and many a weary traveler climbed out of the airplane at Montreal or Toronto after a night in the air and two or three dreary days among

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the sheds on the quays of Liverpool or Southampton. The unfortunate ones who failed to make the transatlantic passage missed not only a stimulating meeting but the gratification of experiencing a warmth of hospitality, as well as of climate, quite foreign, so the visitors said, to those brought up on the chilly shores of the British Isles. In particular the members of the British Medical Association were impressed by the large attendances at the scientific meetings, nearly 2000 being present to hear the speakers at the first plenary session on "The Present Status of Chemotherapy of Bacterial Infections." The round-table conferences were also a novel attraction, for not even the platform speakers were allowed to hold the microphone for more than five minutes, and the rapid fire of question and reply called for an adroitness in debate not usually required at such gatherings as the sectional meetings of the Royal Society of Medicine in London.

It was natural that the Canadians should show a particular interest in the British health service, and that the British doctors should want to know how the Canadian medical services were progressing. At a panel discussion on the National Health Service four British physicians—two general practitioners, a specialist and a medical officer of health—managed to give the impression that the service was working reasonably well, even though it might not be all the medical profession wished it to be. Nevertheless, when Dr. I. D. Grant, the chairman of the Representative Body of the British Medical Association, advised the Canadians to keep politics out of their health service, his remarks were enthusiastically acclaimed. In a thoughtful address given during the meeting, the Honorable Paul Martin, Canadian Minister of National Health and Welfare, said that it was no easy task to find some satisfactory method of extending the protection that the public now had in part against the cost of health care. "Our objective is to work out some scheme that will provide the most effective way of meeting the problem without destroying the fundamental pattern of our society."

The last day of the meeting was given up to a visit to Niagara Falls, which impressed the visitors almost as much as the fact that the busses in which they traveled could hurtle across road intersections against the red lights at 70 miles per hour—given, of course, the privilege of a police escort. Thereafter, many British doctors made their way south to the United States. Some, to their evident pleasure, found themselves in New England for the first time, and were suitably impressed to hear the city of Boston described by the guide of a sight-seeing party as "the greatest hospital center in the world."

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 41331

PRESENTATION OF CASE

A seventy-nine-year-old woman entered the hospital because of jaundice.

Six weeks before admission the patient experienced pain in the right groin and lower abdomen and became constipated. She was operated on at another hospital with a diagnosis of right-sided femoral hernia. She tolerated the operation well, but persistent postoperative vomiting developed. She was not transfused or given plasma, but she did receive fluids intravenously for a few days. X-ray examination at that time revealed a large hiatus hernia, which was reducible under fluoroscopy. After discharge she complained of midepigastric pain after eating, anorexia, nausea and occasional vomiting. Two days before admission her husband noticed that she was jaundiced, and on the day of admission her physician confirmed this and also felt a slightly enlarged liver.

The patient had never been jaundiced previously. Her physician did not think that she ever had symptoms suggestive of gall-bladder disease. She had never taken Thorazine or been exposed to hepatotoxins. She had had vague epigastric pain partially relieved by soda for several years. For about a year she also had had severe back pain, which was thought to be due to osteoporosis. There was no history of melena.

Physical examination revealed a thin, dehydrated and very jaundiced woman complaining of pains all over, especially in the back. Stony-hard, deep cervical lymph nodes were felt on both sides anteriorly. The largest was 1.5 cm. in diameter and was under the insertion of the left sternocleidomastoid muscle. The chest showed slight dorsal kyphosis. There was pain in the region of the sixth thoracic to the first lumbar spine when the patient was sitting up. The breasts were normal. The lungs were clear. The

heart appeared slightly enlarged, and there was a harsh systolic murmur maximal just above and medial to the apex; it was also heard in the aortic region and was transmitted to the axilla and neck. The abdomen showed fullness and dullness in the flanks, but there was no definite fluid wave. The liver was felt 3 fingerbreadths below the right costal margin and was soft, firm, and tender but not nodular. The spleen was not palpable. The extremities were normal.

The temperature was 98°F., the pulse 106, and the respirations 22. The blood pressure was 122 systolic, 80 diastolic.

The urine had a specific gravity of 1.010 and gave a ++ test for albumin and a +++ test for bile; the sediment contained 20 to 30 white cells per high-power field. Examination of the blood revealed a hemoglobin of 11.2 gm. per 100 cc. and a white-cell count of 12,100, with 83 per cent neutrophils. The serum sodium was 121 milliequiv., the potassium 2 milliequiv., and the chloride 70 milliequiv. per liter; the nonprotein nitrogen was 46 mg., the total serum bilirubin 17.2 mg., the albumin 3 gm., the globulin 1.6 gm., and the alkaline phosphatase 84.4 units per 100 cc. (fifteen-minute test). The prothrombin time was 19 seconds (normal, 13 seconds), the thymol turbidity 6.5 units, the thymol flocculation ++, the cephalin flocculation ++++ in twenty-four and forty-eight hours, and the cholinesterase 0.18 delta pH per hour. A finger specimen of stool was clay colored and streaked with red blood; the guaiac test on the stools was negative once and +++ once. X-ray films of the chest demonstrated marked demineralization of the thoracic cage and bilateral elevation of the leaves of the diaphragm. The heart showed probable enlargement in the region of the left ventricle. The pulmonary vascular markings were prominent, and there was minimal fluid in both costophrenic sinuses. There was no evidence of hilar or mediastinal lymphadenopathy. The abdominal films showed that the kidneys were slightly smaller than normal. There was demineralization of the pelvis and lumbar spines and evidence of Paget's disease involving the right os coxa. The other visceral and soft-tissue shadows were within normal limits.

The patient was treated supportively. Two days after admission she became cyanotic during a bout of vomiting and died shortly afterward.

Differential Diagnosis

Dr. Myles P. Baker*: The diagnostic questions center, of course, on the cause of the jaundice and, although there is little evidence to go on, on the manner of death. I think a woman in her eightieth year who has had backache for several months, who later has jaundice and who has palpably enlarged hard lymph nodes in the neck must be presumed to have neoplastic disease unless another disease can be proved.

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The importance of the laboratory tests is considerable because they are the only evidence that I really have to be guided by. She was not particularly anemic, as one would have expected if she had had a malignant process. The white-cell count of 12,000 was higher than one would have expected with intrahepatic infection of the viral sort alone. The electrolyte figures simply indicate depletion, probably as a result of the vomiting. The level of the serum bilirubin was so high that it seems inescapable that this woman had been jaundiced far longer than a few days before admission. The serum albumin level was low, as it is with a decrease in the functioning hepatic parenchymal mass. Inadequate food intake may have contributed to that. The serum globulin level was notably not elevated as it is with intrahepatic parenchymal lesions such as cirrhosis of the liver. The alkaline phosphatase was particularly high — so high that it was reckoned on only a fifteen-minute rather than an hour test; this must be evaluated in the light of the x-ray finding of Paget's disease. Ordinarily, in the presence of Paget's disease, the alkaline phosphatase level cannot be considered dependable in the evaluation of the status of the liver. I suspect here that the elevation of the serum alkaline phosphatase was contributed to by the lesions both in the liver and in the bones. The prolonged prothrombin time probably speaks for hepatic parenchymal disease.

The ++++ cephalin flocculation takes some explaining because ordinarily with obstructive disease, usually malignant, extrahepatic in location and of fairly recent origin, one would not expect to find a ++++ test. I suspect, as I said before, that this woman had been jaundiced considerably longer than a few days; there may well have been time for enough parenchymal handicap to develop to produce a ++++ cephalin flocculation. In an interesting recent review of liver-function tests Hanger† says that the failure of the liver with necrotizing lesions to synthesize the stabilizing factors like the alpha globulins leads to depletion of these factors in the blood and produces the positive cephalin flocculation, which is due to attachment of gamma globulins to cephalin emulsion particles; when there is a ++++ cephalin flocculation, therefore, one should consider failing liver-parenchymal cells that are undergoing autolysis.

I think it is difficult to draw conclusions from the fact that this woman had red-blood streaks on clay-colored stools. The streaking may have been from hemorrhoidal bleeding; it may have been related to the hypoprothrombinemia, which gave a concentration of about 25 per cent, or it may simply have been the unexplained bleeding that one sees with markedly jaundiced patients.

May we see the x-ray films, Dr. Hanelin?

Dr. Joseph Hanelin: The films of the chest demonstrate the elevated diaphragm and some fluid

†Hanger, F. M. Meaning of liver function tests. *Am. J. Med.* **16**: 565-573, 1954.

in each costophrenic sinus. The heart is enlarged although all of it is not visible because of the elevated diaphragm. The enlargement is probably primarily left ventricular fullness. The vessel markings are also increased in prominence. In the abdominal film I think there is evidence of ascites. There is generalized haziness of the abdomen as well as some bulging of the flanks, and in particular there is diffuse density over the true pelvis. I see no evidence of obstruction. The liver edge is prominent on the right. Both kidneys are relatively small, as might be expected in an elderly patient who has some secondary renal contraction.

DR. BAKER: I think the important observation from the x-ray films is that ascites may be present. When an abdominal hernia is discovered and subsequently liver disease is recognized one always wonders whether the production of ascitic fluid has been the factor that has made a hernia of long-standing obvious.

I think that the most likely possibility is that this woman had a cancer; its primary location is, of course, in doubt. The findings in the gastrointestinal series done at the other hospital gave no evidence of cancer of the stomach. I do not know whether she had a small annular carcinoma of the sigmoid that may have been contributing to the constipation. The possibility of carcinoma of the body of the pancreas that later extended into the head of the pancreas and produced extrahepatic biliary obstruction remains. It seems to be a plausible explanation for the presence of back pain, which in so many patients with carcinoma of the pancreas is glibly ascribed to osteoporosis, without proof. Such a cancer in the body and head of the pancreas would probably metastasize to the liver; if it did so it could produce both the ++++ cephalin flocculation and the marked decrease in serum cholinesterase, which is simply another more recently developed test for the integrity of the function of the hepatic parenchymal cells. The figure for the cholinesterase should be above 0.5; it was distinctly diminished in this woman. I prefer such a conclusion — of cancer — rather than a primary parenchymal-cell disorder, with which I should have to put too much emphasis on the liver-function tests — such as the cephalin flocculation and the cholinesterase diminution. The presence of ascites, as suggested by the x-ray films, would certainly be in keeping with such a diagnosis. I believe that she had carcinoma of the body and head of the pancreas, with metastases to the liver.

DR. HOWARD S. FRAZIER: The admitting diagnosis on the Service was that given by Dr. Baker with, in addition, the possibility of gastric carcinoma. Several findings made us change our diagnosis on the discharge sheet. One was the fact that there was a history of childhood tuberculosis, which raised the possibility that the cervical adenopathy could be explained on that basis. Another was the downhill course over a period of forty-eight hours in the hospital from a state of relatively good health until a short time before admission. The third, although this was given less weight than the second, was the evidence from the blood chemical determinations of severe parenchymal involvement. For these reasons the patient was believed to have subacute yellow atrophy.

DR. BAKER: I thought that from the manner of death it was probably due to pulmonary embolization during the vomiting.

DR. FRAZIER: We believed that she had aspirated material.

DR. BENJAMIN CASTLEMAN: Dr. Bartlett, do you have any comments?

DR. MARSHALL K. BARTLETT: I should like to reinforce what Dr. Baker has already said about accepting at face value the appearance of a hernia in an elderly patient. Certainly, that is cause for a careful investigation of the patient's general status before one embarks on what may seem to be a simple surgical procedure.

DR. CASTLEMAN: The hernia being a sign of what?

DR. BARTLETT: It may be a sign of one of various conditions; the commonest one is a large-bowel lesion that has heretofore been unsuspected. Such a lesion makes the hernia increase symptomatically; therefore, it is the hernia that brings the patient to the physician. The routine evaluation of the condition of the large bowel in these cases will occasionally reveal an unsuspected lesion.

DR. BAKER: Particularly when there is an umbilical hernia with underlying ascites.

DR. CASTLEMAN: Dr. Point, have you a comment?

DR. WARREN POINT: I did not see the patient but I think, as the Service did, that the objective evidence was more in favor of overwhelming liver-cell failure although considerations that Dr. Baker mentioned should not be disregarded. The manner of death does suggest aspiration. On the other hand she had extremely low electrolytes, even two days before she died — a potassium of 2 milliequiv., a sodium of 124 milliequiv. and a chloride of 70 milliequiv. per liter; it is not inconceivable, therefore, that she died as the result of electrolyte difficulty, in addition to overwhelming disease. I should put my bet on fulminating intrahepatic infection, cause unknown.

DR. BAKER: The nonprotein nitrogen was not particularly elevated, so that I thought the electrolyte levels were not critical.

DR. GEORGE C. RICHARDSON: What did the pelvic and rectal examinations show?

DR. FRAZIER: They did not help us in the differential diagnosis.

DR. CASTLEMAN: Why do you ask that, Dr. Richardson?

DR. RICHARDSON: I wondered if the patient had a rectal shelf.

CLINICAL DIAGNOSIS

Subacute yellow atrophy of liver.

Dr. Myles P. Baker's Diagnosis

Carcinoma of body and head of pancreas, with metastases to liver.

Anatomical Diagnoses

Adenocarcinoma, Grade 2, of head of pancreas, with involvement of common bile duct and retroperitoneum and with metastases to liver, lymph nodes, adrenal glands, kidneys, lungs and cecum.

(Jaundice.)

Renal phlebothrombosis, bilateral, due to tumor infiltration.

Ascites (800 cc.).

Hydrothorax, bilateral (600 cc. on each side).

Pathological Discussion

Dr. Castleman: Just before this patient died, the surgeons had planned, as the first step in making the diagnosis, to remove one of the lymph nodes in the neck; however, she failed so rapidly that they did not have time to carry out their plans. At autopsy we found that the diagnosis made by Dr. Baker was correct: that she had a carcinoma of the head of the pancreas, with extensive involvement of the common bile duct, which was almost completely occluded by the carcinoma. The carcinoma had produced a huge mass that extended into the retroperitoneal area — not low enough, Dr. Richardson, to produce a rectal shelf — close to the vertebral column. It had also extended upward through the diaphragm to involve the mediastinum, without involving the lungs themselves. There were metastases to many organs including small metastases to both kidneys and both adrenal glands. Interestingly enough one of the renal veins was completely thrombosed with a tumor thrombus that had extended into it from the retroperitoneal area. The liver weighed only 1300 gm., had only half a dozen metastases and showed no parenchymal damage except for severe bile stasis. There was certainly nothing that I should have supposed would have produced the ++++ cephalin flocculation; I do not know how to account for that. I do not know exactly what the cause of death was unless it was an electrolyte imbalance as Dr. Point suggested. The cause of the blood in the stools was found — a carcinoma in the cecum, which I believe was a metastasis from the carcinoma of the pancreas, for they both had the same histologic picture. The carcinoma had involved the entire wall and eroded the mucosa.

Dr. John T. Quinby: What were the nodules in the neck?

Dr. Castleman: They were metastatic carcinoma. There were no metastases to the vertebras. I think the back pain was due to the retroperitoneal lymph nodes, which involved the celiac axis and all the nerves along the vertebral column.

CASE 41332

Presentation of Case

A sixty-four-year-old widow entered the hospital because of weakness.

Eight months before admission she began to vomit most of the food and fluid she consumed. The vomitus contained no blood. Her weight fell from 120 to 80 pounds, and she became increasingly weak. She complained of occasional epigastric, right-upper-quadrant and severe back pain during this period. Because of weakness she was bed ridden during the three weeks before admission.

The patient had had profuse night sweats requiring changes of night clothes for the past several years. She had had no chronic cough, hemoptysis or pleuritic type of chest pain. She had been constipated for years. She had been a very heavy drinker for years and continued to drink during the present illness. There was a history of three childbirths, which were either stillbirths or were followed by death during infancy.

Physical examination revealed a weak, emaciated woman who was extremely lethargic and only partially oriented. The skin was dry. There were no spider angiomas. The heart was enlarged 3 cm. to the left of the midclavicular line. The aortic second sound was resounding and greater than the pulmonic. There were a Grade 2 aortic systolic murmur transmitted to the neck, a Grade 3 aortic diastolic blowing decrescendo murmur loudest in the aortic area and transmitted along the left sternal border and no mitral murmurs. Crackling rales were heard at the right apex. The right hemithorax was dull, with diminished breath sounds. The diaphragm appeared to be low by percussion. The liver was palpable 5 fingerbreadths below the right costal margin, and was firm and nontender. The spleen was not palpable. Neurologic examination was negative except for slight delirium.

The temperature was 98.8°F., the pulse 76, and the respirations 16. The blood pressure was 110 systolic, 45 diastolic.

Urinalysis was negative; the pH was 5.5. Examination of the blood showed a hemoglobin of 13.6 gm. per 100 cc. and a white-cell count of 9700, with 68 per cent neutrophils. The bilirubin was 0.8 mg., the nonprotein nitrogen 55 mg., the albumin 1.8 gm., the globulin 2.2 gm., and the alkaline phosphatase 21.3 units per 100 cc.; the sodium was 125 milliequiv., the potassium 3.4 milliequiv., and the chloride 86 milliequiv. per liter. The cephalin flocculation was +++ in twenty-four and ++++ in forty-eight hours, and the prothrombin time 16 seconds (normal, 13 seconds). A blood Hinton test was positive. A lumbar puncture revealed that the cerebrospinal fluid was under an initial pressure equivalent to 45 mm. of water and contained 7 mononuclear cells per cubic millimeter, with a total protein of 20 mg. and a sugar of 83 mg. per 100 cc., and a gold-sol curve of 0012211000. Three sputum smears were nega-

tive for acid-fast bacilli. Two stools showed a negative guaiac test. An electrocardiogram was within normal limits. X-ray films of the chest showed scattered, fine mottling throughout both lung fields and a soft, ill defined area of increased density in the apical posterior segment of the right upper lobe. There were marked emphysema and denting of the right leaf of the diaphragm. The aorta was tortuous and calcified in the ascending and descending portions. The bones were osteoporotic. Films of the spine revealed a wedge-shaped second lumbar vertebra, with marked flattening and angulation secondary to a fracture. There was no evidence of bone destruction. The abdominal aorta was markedly calcified. An abdominal film showed a normal gas pattern and no evidence of soft-tissue masses.

On the second hospital day the patient was severely ill, and the temperature rose to 102°F., the pulse ranged between 80 and 90, and the respirations between 23 and 32. She was extremely toxic on the next day and had a temperature of 104°F. She complained of pain in the anterior part of the chest on deep breathing. The white-cell count was 9000, and penicillin was started. On the third hospital day the temperature was 103°F., and the pulse 120. Soft, crepitant rales were heard at the left scapular angle and at the right apex anteriorly and posteriorly. The basal diastolic murmur increased considerably in intensity, and a medium-pitched diastolic blow was audible at the apex. Systolic murmurs were heard at both base and apex. There were no petechiae or splinter hemorrhages.

A diagnostic procedure was performed on the fourth hospital day.

Differential Diagnosis

Dr. Farahe Maloof*: In summary this sixty-four-year-old woman entered the hospital because of weakness, vomiting, marked weight loss, pain in the upper abdomen and night sweats for from eight months to two years. After reading the protocol I thought that the diagnosis would depend a great deal on the x-ray films, but Dr. Hanelin tells me that they are missing.

Dr. Benjamin Castleman: Since the films are missing I might read the interpretation of the chest films given in the record: "The picture of the chest is that of a miliary disease; tuberculosis should be considered."

Dr. Maloof: Several diagnoses are obvious, and I might discuss these first. She apparently had syphilis as evidenced by the positive blood Hinton test, the past history of three presumed stillbirths, the classic signs of aortic insufficiency and the calcification in the ascending aorta. The only information lacking is a spinal-fluid Hinton test. However, there is no clinical evidence for central-nervous-system syphilis. The manifestations of syphilis probably played no part in the terminal event. No mention was made of any therapy for syphilis in the past.

Dr. Robert E. Scully: Spinal fluid was sent to the State Laboratory, but it was insufficient in quantity to be tested.

Dr. Maloof: I am surprised that the electrocardiogram was within normal limits in view of the cardiac and the pulmonary abnormalities.

The next fairly obvious diagnosis is cirrhosis of the liver. She was a heavy drinker, and the tests of liver function are certainly compatible with a fairly severe degree of liver insufficiency. The alkaline phosphatase is out of line, for it was elevated to a higher level than one would expect with cirrhosis and suggests infiltration of the liver with tumor or some other process. The elevated alkaline phosphatase, of course, may have been related to some bony abnormality such as Paget's disease, which is common in this age group. There was collapse of the second lumbar vertebra, but apparently there was no bone destruction. The bones were said to be osteoporotic, which I suppose, in this patient, was related to the menopause. This is a fairly common area for the collapse of a vertebra to occur in patients with menopausal osteoporosis.

I am not sure that the liver was really enlarged although it was said to be 5 fingerbreadths below the right costal margin, for on percussion the leaf of the diaphragm appeared low. Hepatic enlargement in this patient would be consistent with cirrhosis or an infiltrative process. No mention was made of nodules in the liver. In the interpretation of the plain film of the abdomen nothing was mentioned about the size of the liver and the spleen. I am interested in the size of the liver, for if it was enlarged I should wonder about hepatoma accompanying the cirrhosis. The elevated alkaline phosphatase, the subsequent course of events and the fever would be consistent with a diagnosis of hepatoma, which could also explain the pulmonary findings. However, I am not sure that I have enough evidence on which to make a diagnosis of hepatoma. Often, with the development of hepatoma, there is severe decompensation of the liver and a great deal of ascites. No ascites or peripheral edema was noted on physical examination.

She had abdominal pain, which occasionally was located in the epigastrium. I suppose that this might be gastritis in an alcoholic patient. I do not know how to tie in the right-upper-quadrant and severe back pain. This type of pain may be seen occasionally in patients with cirrhosis, but it is supposed to be more characteristic of hepatoma superimposed on cirrhosis of the liver. The pain was not persistent. If the back pain was over the lumbar area, it could be explained easily by the collapsed lumbar vertebra, which I shall have to assume was related to the osteoporosis.

Another possibility to explain the upper abdominal symptoms is carcinoma of the pancreas that spread to the liver. Carcinoma of the pancreas frequently

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metastasizes to the lung. I remember reading a case that Dr. John W. Cass[1] discussed here about ten years ago in which the patient had both pancreatic carcinoma, with spread to the lungs, and miliary tuberculosis. Both of those diagnoses should be considered in this patient. I cannot establish the diagnosis of carcinoma of the pancreas. It seems to me that a gastrointestinal series must have been done in view of all the vomiting. Was it done?

DR. CASTLEMAN: No.

DR. MALOOF: The blood chemical levels were interesting — namely, the low serum sodium and chloride, the elevated serum nonprotein nitrogen and the low normal serum potassium. I am not told about the pH or the carbon dioxide content of the blood. The symptoms of weakness, vomiting and weight loss suggest adrenal insufficiency, but these chemical levels per se do not establish a diagnosis of Addison's disease. No mention was made of any abnormal pigment in the skin or in the buccal mucosa. Also, the pH of 5.5 in the urine is against such a diagnosis, for patients with Addison's disease are usually unable to produce an acid urine. These chemical levels might be related to the vomiting and poor nutrition of the patient, but they are also seen in patients with pulmonary disease, usually pulmonary tuberculosis, who are termed "pulmonary salt wasters." Frequently, such patients are suspected of having Addison's disease, but tests of their adrenal functions are normal.

The terminal event occurred rather suddenly, with a rise in temperature and pulse and deterioration of the patient. These signs have been described in alcoholic patients who die suddenly without any apparent cause.

The pain in the anterior part of the chest, which was worse on deep breathing, was obviously pleurisy, but whether the pleurisy was due to an infection or not is difficult to say. The white-cell count did not change. She could have had a pulmonary infarct. However, on the basis of the data that are presented, it is difficult to make that diagnosis. There was no mention of cough or hemoptysis. The physicians in charge were considering subacute bacterial endocarditis, for they noted that the heart murmurs increased in intensity and that a murmur suddenly developed at the apex of the heart. Perhaps the latter was an Austin-Flint murmur, which may become audible when heart failure develops. More rales were heard in the chest at this time, but I cannot be sure whether they were the result of heart failure or of an increase in the underlying pulmonary disease. No mention was made of the appearance of the neck veins.

One should always consider the diagnosis of tuberculosis in an alcoholic patient who has pulmonary disease. I shall assume that the lung findings looked like miliary tuberculosis since the description seems to fit. The presence of the 7 mononuclear cells in the spinal fluid suggests meningeal irritation, possibly tuberculous meningitis. Patients with miliary tuberculosis may have no clinical signs of meningeal involvement, and yet analysis of the spinal fluid may reveal an increased number of cells, with no other findings. If this cerebrospinal fluid is allowed to stand, a pellicle may form, and this can be stained and examined for acid-fast bacilli. The enlargement of the liver could be explained by infiltration with tuberculosis.

In summary I shall say that this patient had syphilis with aortic insufficiency, cirrhosis and questionably a hepatoma of the liver and miliary tuberculosis with involvement of the meninges, the lungs and the liver. Pancreatic carcinoma with metastases to the lungs is a possibility. I have to theorize about the diagnostic procedure; unless a bone-marrow aspiration was done I believe that a needle was put in the liver.

DR. SCULLY: This patient was a diagnostic puzzle. She lived alone and was a very unreliable informant. Most of the history was obtained from neighbors.

Would anyone like to comment?

DR. MALOOF: I should like to know about the pain in the anterior part of the chest. Did anyone hear a friction rub or a pericardial rub?

DR. SCULLY: There was no mention of a friction rub in the record.

DR. CASTLEMAN: Dr. Stokes, a cardiologist from Sydney, Australia, is here. Perhaps he would like to comment on the heart signs.

DR. E. H. STOKES: The heart signs are indicative of syphilitic aortic disease. I do not believe that the murmur was an Austin-Flint murmur, which is usually described as being a presystolic type of murmur at the apex. The murmur that is described here was diastolic in type and was at the base.

DR. MALOOF: Would you care to make an additional diagnosis of rheumatic heart disease?

DR. STOKES: Not in this case.

CLINICAL DIAGNOSES

?Miliary tuberculosis.
?Cirrhosis of liver.
?Carcinoma of pancreas with metastases.
Syphilitic aortitis.

DR. FARAHE MALOOF'S DIAGNOSES

Syphilitic aortitis, with aortic insufficiency.
Cirrhosis of liver, ?hepatoma.
Miliary tuberculosis, with involvement of meninges, lungs and liver.

ANATOMICAL DIAGNOSES

Miliary tuberculosis.
Syphilitic aortitis, with aortic insufficiency.

PATHOLOGICAL DISCUSSION

DR. SCULLY: The diagnostic procedure was a punch biopsy of the liver. The specimen showed a

large number of granulomas histologically compatible with either sarcoidosis or miliary tuberculosis. With this finding the clinicians placed the patient on chemotherapy, consisting of PAS, streptomycin and isoniazid. The subsequent course was complicated by some interesting neurologic developments. I shall ask Dr. Lapham to tell us what happened in the last two weeks before death.

DR. LOWELL W. LAPHAM: During the first few days after the liver biopsy there was relatively little change in the patient's status. Two days after the

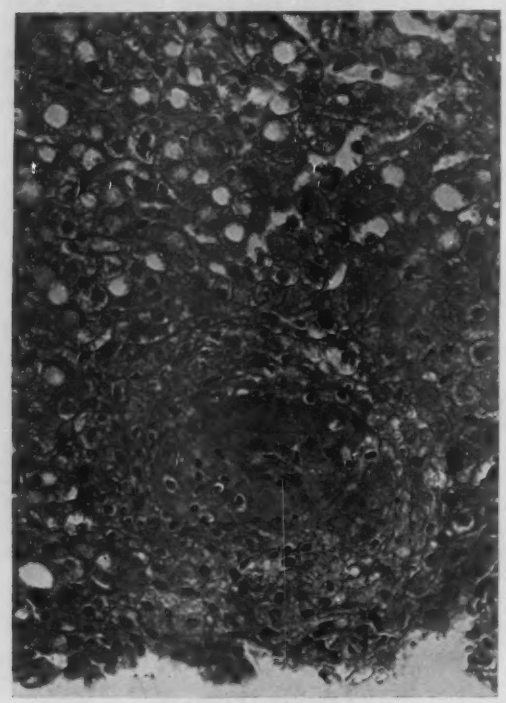

FIGURE 1.

liver biopsy a lumbar puncture was performed; the tap was traumatic. The fluid contained 3000 red cells and 300 white cells per cubic millimeter, of which 95 per cent were considered to be lymphocytes. The total protein was 38 mg. and the sugar 82 mg. per 100 cc. (a simultaneous blood sugar was 78 mg. per 100 cc.), and the chloride 94 milliequiv. per liter. Three days later the lumbar puncture was repeated; the initial spinal-fluid pressure was equivalent to 160 mm. of water. The fluid contained 260 cells, of which 258 were red cells and only 2 were lymphocytes. The sugar was 76 mg., and the total protein 14 mg. per 100 cc., and the chloride 108 milliequiv. per liter.

Eight days after the liver biopsy the patient began to exhibit seizures on the right side of the body that were described as clonic in character. They had the unusual feature of beginning with muscular twitchings of the right side of the abdomen, spreading downward into the right lower extremity and upward to the face. These seizures were intermittent at first, lasting several minutes at a time, but by the next day they were continuous, consisting of clonic movements of the right side of the body. At times they extended over to the left side, particularly to the left leg, but usually they remained on the right side. Continuous movements of flexion and extension of the right arm and leg were noted. She was able to talk during the seizures and was described as being mentally dull and confused. Responses to spoken commands and questions were slow, and speech sometimes was relevant and sometimes irrelevant. She did not exhibit any focal signs other than the seizures, except for a positive Babinski sign on the right. However, on the next day, bilateral Babinski responses were noted. She was placed on intensive anticonvulsant therapy, with some but not complete control of the seizures. Her general condition deteriorated only slightly during the next few days. On the twelfth day after the liver biopsy, she was found in coma. Examination at that time revealed a profound state of coma; she was not responsive even to

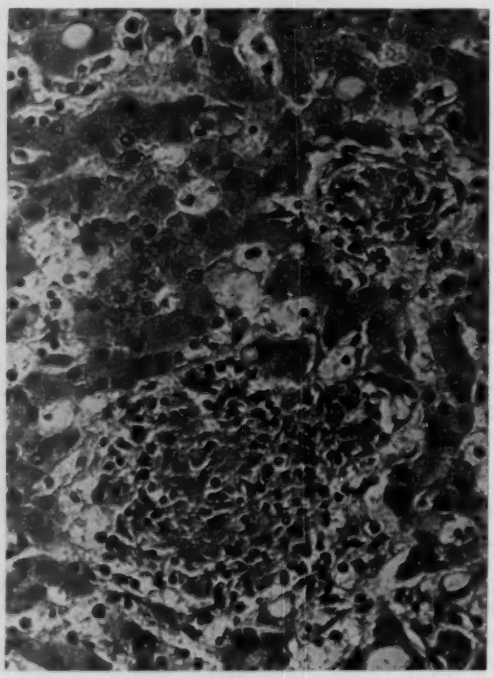

FIGURE 2.

painful stimuli. Respirations were intermittently Cheyne–Stokes in character. The seizures had completely disappeared. She was covered with a diffuse, macular rash. She continued to exhibit bilateral Babinski signs. The lumbar puncture was repeated. The cerebrospinal fluid was under a pressure equivalent to 165 mm. of water and was clear. It contained 3 lymphocytes per cubic millimeter and gave a negative

Pandy test. During the next twelve hours the patient's condition steadily declined, and respirations ceased twelve hours after the onset of coma.

DR. SCULLY: At autopsy there was miliary tuberculosis involving the lungs, liver and spleen, and to a lesser extent other organs. The right pleural cavity was obliterated by dense fibrous adhesions. There was more tuberculosis in the right upper lobe than in the other portions of the lungs. There was a syphilitic aortitis, with involvement of the aortic valve, and slight cardiac hypertrophy (the heart weighed about 320 gm., which is large in a woman of her small size).

The punch-biopsy specimen of the liver showed large numbers of granulomas and a moderate amount of fatty metamorphosis, but no cirrhosis (Fig. 1). The granulomas were composed of Langhans giant cells and epithelioid cells, and were surrounded by thin rims of chronic inflammatory cells. The autopsy specimen of liver, on the other hand, showed a somewhat different microscopical picture (Fig 2). Here were large numbers of chronic inflammatory cells, but almost no well formed granulomas. Although some of the difference in the appearance of the specimens was undoubtedly due to the fact that one was post mortem and the other surgical I do not believe that this factor alone is an adequate explanation. One must assume, I think, that the chemotherapy played some part in changing the character of the pathological response.

There was no cirrhosis. However, throughout the liver there was inflammatory-cell infiltration, most intense around the small bile ducts. I think that this diffuse hepatitis accompanying the miliary tuberculosis probably damaged the liver sufficiently to cause the abnormalities in liver function.

DR. MALOOF: Was the calcification in the abdominal aorta syphilitic or arteriosclerotic?

DR. SCULLY: The disease in the ascending aorta looked like a typical syphilitic aortitis; that in the descending aorta was no more marked than we often see in pure atherosclerosis although it certainly may have had a syphilitic background in this particular case.

Dr. Richardson will tell you about the findings in the central nervous system.

DR. EDWARD P. RICHARDSON, JR.: Examination of the brain yielded no evidence whatsoever of a generalized meningitis. This was entirely compatible with the spinal-fluid findings. Likewise, sections of the brain did not disclose an ependymal reaction suggesting an inflammatory process, either tuberculous or syphilitic, so that both syphilitic and tuberculous meningitis can be thereby ruled out. As in other organs, there were in the brain several miliary granulomas, which were typical caseous tubercles. One of these was situated in the hippocampal formation on the right side, one in the right and one in the left cingulated gyrus posteriorly, and one at the base of the pons on the left side in the pyramidal tract. I think it is difficult to explain the nature of the seizures on the basis of the lesions that were found. We did not find any lesions on gross examination in the classic motor area. One can only assume that one or another of these cortical lesions acted as an irritative focus and that the seizure pattern was determined by factors that are not quite clear.

Some years ago Rich and McCordock,[2] at Johns Hopkins Hospital, carried out studies that revealed that miliary tuberculosis is not necessarily productive of tuberculous meningitis, and may often not be. In their large series of cases they found the typical neurologic manifestation of miliary tuberculosis to be scattered tuberculomas, chronic discharge of infected material directly into the subarachnoid space over a considerable period being necessary to produce a diffuse proliferative and exudative meningitis typical of tuberculous meningitis.

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The New England Journal of Medicine

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY

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THE CANADIAN MEETING

A SHORT report in this week's "Medical Intelligence," written especially for the *Journal* by Dr. John W. P. Thompson, deputy editor of the *British Medical Journal,* outlines entertainingly some of the high spots in the recent joint meeting of the British, the Canadian and the Ontario medical associations. The convention, which was held in Toronto from June 20 to June 24, was, with a grand total of 4529, the most largely attended medical gathering ever to take place in Canada. The official figures, when broken down, record the registration of 3071 members of the Canadian Medical Association and 370 representing the British Medical Association, accompanied by 100 British and 988 Canadian consorts.

Nearly 1000 members, according to the *British Medical Journal,* attended the annual dinner at the Royal York Hotel, presided over by the incoming president of both the British and the Canadian associations, Dr. Clarence Routley, of Toronto. In his address on this occasion Dr. Routley told of his clerkship in an insurance office nearly fifty years ago, before he had studied medicine, where he was given a financial statement to check. For this responsible task he was paid 75 cents and later discovered that he had audited the accounts of the 1906 Toronto meeting of the British Medical Association. Whether this experience enticed him into medicine or drove him there he did not say.

The Honorable Paul Martin, Canadian Minister of National Health and Welfare, in proposing a toast to the B. M. A. on this occasion characterized the medical profession as an important unifying factor in the British Commonwealth. The national medical associations, he believed, "had provided a pattern of respect for the rights of others and a devotion to high ideals by providing leadership in a field of social importance."

UNDER THE BIG TOP

THE Program Committee for the 1955 American Medical Association Clinical Session to be held in Boston this fall is apparently on the road to establishing some sort of record in the way of effective preparation for such events. Whereas in the past the clinical sessions have been organized in co-operation with state and local committees, this one is for the first time an areal enterprise, in addition to being a national one, in the plans for which all the New England States are participating.

The arrangement of a balanced scientific program to occupy three and a half days is no small task, and many meetings and much correspondence have continued to occupy the Committee during a summer that has established, at the date of writing, a seventy-year record for heat and humidity. Topics that will

be discussed by the foremost authorities in the country range from the art of medical practice to the use of the cortisones; from the presentation of clinicopathological cases according to the patterns in vogue at the Massachusetts General and Peter Bent Brigham hospitals to the control of hepatitis and the causes and prevention of developmental defects.

Emphasis again falls on a special feature of the session — the daily closed-circuit color television programs from the New England Deaconess Hospital. The morning programs will present surgical procedures by staff members of the hospital, whereas those presented in the afternoons will be medical in nature; they will be put on the screen in a special hall in Mechanics Building through the generosity of Smith, Kline and French Laboratories of Philadelphia.

Participation in the afternoon programs, as previously announced in these pages, is open to all, subject to acceptance by the Television Committee, of which Dr. Alexander Marble, 81 Bay State Road, Boston 15, is chairman. Although the time is approaching when this offer must be closed, suggestions for presentations of unusual merit, summarized in not more than 300 words, may still be considered by the Committee.

POLIO PANIC

THE country's most distinguished victim of infantile paralysis, and certainly a courageous one, once tried to impress upon the American people the fact that fear was the most corroding influence that could affect their lives. These words of President Roosevelt, spoken at a time of crisis when many Americans believed that they had much to fear, helped stiffen the will of the nation to the point of a determined and in many cases a heroic resistance to a grave danger that threatened all. Unfortunately, a contagious mass hysteria, nourished by practically every agency of public communication, has caused countless persons to capitulate to an unreasoning dread of the very affliction that Mr. Roosevelt so nobly overcame.

Paralytic poliomyelitis, whether fatal or not, is a distressing disease, and extraordinary efforts are being made toward its prevention and amelioration. Poliomyelitis, however, needs to be viewed in its proper perspective — in its true relation to the other disturbances that affect mankind. The 100,000 unfortunate victims each year of the paralytic form of the disease should be considered in relation to the 160,000,000 persons who escape it, — at least in a recognizable form, — to the 200,000 current sufferers from muscular dystrophy, the 250,000 with multiple sclerosis, the 400,000 with tuberculosis, the 600,000 with cancer, the 2,500,000 under treatment for mental disease, the 7,500,000 with arthritis and rheumatism, and the 16,000,000 or more with some form of heart disease.

The emotional reaction to poliomyelitis, distressing as are both the reaction and the illness, should be considered in relation to such common experiences as riding in an automobile, an adventure that cripples or destroys far more human beings each year than does poliomyelitis, and yet one that is entered upon carelessly and often with pleasurable anticipation.

When one hears of offices being closed in panic because of the occurrence of a case of poliomyelitis among the personnel, of a frantic mother bringing a sobbing child to her physician, parent and offspring equally afraid that a mild indisposition might be poliomyelitis, one wonders what has happened to a people's sense of proportion, its ordinary judgment and its fortitude in times of limited stress.

A Singular Case — A Ball Lodged for Fifty Years. — *There has just died, in the village of Reindorf, in France, in his seventy-fifth year, a veteran of the French army, M. Peter Klein, who, at the battle of Austerlitz, on the 2d December, 1805, was struck by a Russian musket-ball, which lodged in the left temple, just above the ear, and remained there until the day of his death, a period of nearly fifty years, without having caused him any pain, or at all affected his intellectual faculties.*

Boston M. & S. J., *August 23, 1855*

MASSACHUSETTS MEDICAL SOCIETY

JOINT COMMITTEE ON IMPROVEMENT OF PATIENT CARE

The following informal report of the Joint Committee on Improvement of Patient Care has been submitted for publication by the chairman, Dr. Maurice Fremont-Smith.

In 1948, initiated by the American Hospital Association, a National Commission on the Care of the Patient was founded. This Commission included representatives from the American Medical Association, American Hospital Association, American Nurses Association, and the National League for Nursing. It was the expressed wish of this National Commission that similar State committees be set up to discuss subjects pertaining to patient care. In 1954, therefore, Dr. Bonnet, representing the Massachusetts Hospital Association, requested the president of the Massachusetts Medical Society to establish such a committee and invite the Massachusetts Nurses Association and the Massachusetts Hospital Association to name representatives.

The State Committee has held eight meetings. It early recognized that, healthy and valuable as its frank discussions proved to be, similar discussions between the three groups — doctors, nurses and administrators, on the actual field of battle (i.e. in each hospital) was the primary need. Some doubts were expressed as to whether doctors would attend such hospital meetings, but the

Committee was confident that, if the doctors found such hospital meetings to be effective, they would loyally serve in the interest of better patient care.

The State Committee, therefore, invited 12 Massachusetts hospitals to form trial inter-departmental committees, and requested periodic reports from these hospitals.

We have reports to date from eleven hospitals. All attest to the value of these Committees. One hospital administrator writes, "Once each group begins to appreciate the problems of the other, when certain resentments and prejudices can be candidly expressed and calmly discussed in an atmosphere of mutual respect, the patient cannot help but be better cared for."

Subjects discussed at the hospital level have included such specific problems as:

(1) Doctor's orders: written and verbal
(2) Special diets
(3) Treatment of bed sores — whose responsibility? nurses' or doctors'?
(4) Isolation techniques

Also, and perhaps more important have been discussions of more general problems which tend to solve themselves when each group understands the difficulties of the others.

In one hospital several meetings were devoted to a questionnaire to be presented to patients on discharge — items included the following questions: Did the nurse or attending personnel explain to you what they were going to do when they came to give you treatments — or an unfamiliar procedure prescribed by your doctor? Did your doctor explain to you in advance about any treatment which he gave you? Were you allowed to eat your meals without interruption?

Several hospital administrators emphasized that care is necessary in setting up such committees, to be certain that the proper people are invited to serve; and that medical staff participation and active liaison with the medical staff are essential to successful function. In other words, the job cannot be done by nurses and adminstrators to, or for, doctors. It can only be done *with* the doctors.

Meanwhile, the State Committee has been meeting regularly and has spent much of its time wrestling with the following problems:

(1) What is essential patient care?
(2) What are the responsibilities of the doctor in total patient care?
(3) What unnecessary procedures are part of average hospital routine?
(4) What are the duties of a nurse? What do doctors (and patients) expect of a nurse?
(5) What should be the doctor-nurse relationship in the care of the patient?

In regard to the last question, three propositions were presented to the Committee for discussion:

Proposition 1. The nurse is solely the agent of the doctor in all relations with the patient, and has no area of independent decision except by implied or explicit delegation from the doctor.

Proposition 2. The nurse and the doctor are partners in the care of a patient. Each has his or her own area of concern in which each is autonomous — the doctor functioning primarily in the field of specific treatment, and using the technical assistance of the nurse — the nurse functioning primarily in the field of general care of the patients' physical comfort and well-being, including emotional support.

Proposition 3. The nurse has a primary role in creating the climate in which a doctor functions, and the doctor only acts when access to the patient is consented to by the nurse who has become a substitute parent. In the doctor's decisions involving specific treatment, he acts alone but only at times arranged by the nurse.

The Committee has arrived at no conclusion as to which of these propositions — or combination of propositions — expresses the ideal nurse-doctor relationship, but feels that this is an area in which frank discussion will serve to clarify a presently confused area.

Bearing on this question of doctor-nurse relationship is the problem of the curriculum offered nurses in the training schools. Considerable discussion of this subject has been held in the State Committee. Of interest in this regard are the results of a questionnaire sent out by a group of nurses to some 300 doctors, asking what the doctor expects of the nurse. Answers were received from 156 doctors. Results were not completely tabulated at our last meeting, but it is the writer's impression that the doctors were, on the whole, satisfied with what the nurse does, and with her training. But the Committee has the impression that the nurses and administrators are not so happy about the doctors. The doctors are often careless about establishing liaison with the nurses at the bedside level. They seldom outline their over-all plan of treatment of the patient. They may neglect to give essential orders, or to cancel orders no longer needed. They frequently order unnecessary special diets (in some hospitals 60% of patients are on special diets), they are sometimes indifferent as to the effect of their words (or their silence) upon the individual patient, leaving it to the nurse to clear up anxiety or misunderstanding caused by the physician or surgeon. Waste of hospital money through unnecessary laboratory or x-ray examinations make added work for personnel and create administrative problems.

It is only through inter-communication between the three groups involved that such misunderstandings and conflicts may be solved. This inter-communication can be and should be the function of the local hospital committees. Problems will always be present, but, as one hospital administrator wrote to the Committee: "It is my belief that, if you can get these people working together, the problems seem to shrink in size."

The State Committee believes that better understanding between the three groups is essential, not only at the bedside, and at the local hospital level; but is equally necessary at State and National levels. As an example of near-breakdown in co-operative action at the State level was the recent introduction by the nursing groups of a bill in the Massachusetts legislature, a bill which was until recently opposed by the Massachusetts Medical Society. Here the doctors were early asked by the nurses for counsel and help, and such help was not forthcoming. So, for the moment we contemplated the nursing group in political conflict with the doctors. Such conflict between closely associated groups devoted to the same cause would have been a tragedy. This was fortunately averted by the action of the Council of the Massachusetts Medical Society. Nurses, doctors and administrators are partners. We have a common objective: the better care of the patient. Only through co-operation at the levels of the bedside, of the hospital, and of the State will this objective be attained.

CIVIL DEFENSE AGENCY

BURN OF THE RETINA IN ATOMIC EXPLOSION

In assessing the ocular significance of the awe-inspiring flash that heralds an atomic explosion one must consider briefly both the physiology of vision and the anatomy of the retina. It will thus be pos-

sible to gain a vantage point from which a clear view of the pathologic processes to be encountered will be obtained.

During adaptation to light many changes take place in the eye. Constriction of the pupil occurs via direct and consensual pupillary reflexes, and there is diminished sensitivity of the retina with bleaching of visual purple, which is the photosensitive pigment. The pH of the retina shifts from alkaline to acid, which is associated with katabolism of glucose.

The retina itself is composed of ten separate layers, and the layer of rods and cones is the one of visual reception. The rods and cones lie with long axis perpendicular to the surface of the retina. The rods contain visual purple, or rhodopsin, and function in dim light (scotopic vision). The cones, on the other hand, are active in bright light (photopic vision). In the human retina there are approximately 115,000,000 rods and 7,000,000 cones, and the light that impinges on the retina to meet the rod-and-cone layer must pass through all other layers. The fovea is composed entirely of cones and is the region where photopic vision reaches its highest state of efficiency.

The high-intensity, brief, radiant heat stimulus of the atomic flash produces the so called "flash burn." The severity of the burn is proportional to the energy flux per unit area of surface exposed. With skin burns the radiant heat dose decreases with the square of the distance from heat source. In the eye, however, the light rays entering the pupil are focussed to an image on the retina. It is thus apparent that the amount of energy absorbed by the retina will be much greater than that penetrating the skin.

The minimal amount of energy necessary to produce a retinal burn is 0.15 gm. calorie per square centimeter. During daylight the pupil admits only 1/50th of the amount of light that the widely dilated pupil admits at night. The danger of retinal burn from atomic flash, therefore, is much greater at night. An energy dose of 80 gram calories per square centimeter would be received with a pupil of 0.4-cm. diameter during daylight; however, at night, a 300-gm.-calorie dose per square centimeter would be received.

The peak of intensity of radiation resulting from an atomic explosion is reached within 1/10,000th of a second at a distance of 15 miles. The latent period of the pupillary and blink reflexes is 1/10th of a second. Therefore, before the eyelids, hands or any protective mechanism could be utilized, retinal burns would be received. Retinal burns have been sustained in rabbits at the Nevada Proving Grounds up to a distance of 40 miles from the site of atomic explosion. The rabbits used in the Nevada test had pigmented ocular fundi, because light absorption by the retinas of such rabbits is similar to that occurring in the human fundus.

The pathologic manifestation in the retina after atomic flash burn is a localized coagulation necrosis in the area where the image is formed on the retina. Healing of flash burn is by sequestration of necrotic cells rather than by organization, which is noted with moderate temperature burns. On ophthalmoscopic examination the lesion appears as a well demarcated, circumscribed area with a deep central crater having a white base. Surrounding this central crater is a gray-discolored mass approximately twice the diameter of the crater. The remaining portion of the retina appears normal. A similar condition has been found in "eclipse burns."

The preventive measures that can be taken against the ill effects of atomic flash burns on the human eye are of extreme importance. These protective measures such as appropriate shelter, covering of the eyes and the use of effective goggles should be taken before the flash occurs, for otherwise irreversible damage to the retina, with permanent blindness, will result. Protective measures taken after the flash are of little value.

THOMAS F. MAHER, M.D., D.P.H.
Executive Medical Officer

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CORRESPONDENCE

REOPERATION FOR GASTRIC ULCER

To the Editor: The death of the seventy-nine-year-old man referred to in my article, "Review of Fifteen Years' Experience with Gastrectomy in a Community Hospital. I. Ulcer," in the August 4 issue of the *Journal*, might have been averted by immediate reoperation in the seventh postoperative day. The need for immediate reoperation and excision of the excluded bleeding ulcer was recently emphasized by Welch, Allen and Donaldson in their paper entitled "Surgical Management of Massive Acute Upper Gastrointestinal Hemorrhage" in the June 2 issue of the *Journal*.

PAUL R. HINCHEY, M.D.
Salem, Massachusetts

ANOTHER MOUNTAINEERING PHYSICIAN

To the Editor: I read with a great deal of interest Dr. Henry R. Viets's article, "Mountaineering Physicians," in the June 23 issue of the *Journal*. I should like to call attention to a very prominent omission: Charles Evans, F.R.C.S., neurologic surgeon from Liverpool. As may be remembered, Charles Evans was picked for the first assault team on the successful ascent of Mount Everest in 1953. He was also deputy commander of the Everest Expedition. He climbed to within 800 feet of the summit and turned back because of lack of oxygen. But the trail he broke helped Hillary and Tenzing a few days later when they reached the summit.

Evans learned his rock climbing in Wales. He had participated in three expeditions to the Himalayas in the three years preceding the successful climb. In 1954 he, Hillary, George Lowe and others returned to do exploration in the lower regions of the Everest region. It will be recalled that

he was the leader in the successful climbing for the first time of Mount Kachenjunga, the fourth-highest peak in the world, within the past month.

I had the opportunity of entertaining the Hillary group overnight on their American tour and found them to be a wonderful group of men. We entertained Evans by showing him a cesarean section, which is somewhat out of his line to be sure.

ROBERT H. GOODWIN

New Bedford, Massachusetts

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Endokrinologische Psychiatrie. By M. Bleuler, professor of psychiatry in Zürich. 8°, cloth, 498 pp., with 30 illustrations. Stuttgart: Georg Thieme, 1954. DM 46.50. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

The author considers general considerations (including the endocrine psychosyndrome), psychopathology of endocrine disturbances and endocrinology of psychic disturbances (schizophrenias, manic-depressive psychosis, organic mental disorders and the endocrinology of psychopathic and neurotic conditions). The literature is thoroughly reviewed. There is a bibliography of 2717 references, as well as indexes of authors and subjects.

Proceedings of the First World Conference on Medical Education, London, 1953: Held under the auspices of the World Medical Association. 8°, cloth, 804 pp. London: Oxford University Press, 1954. $16.00.

At this important congress four opening addresses were made: by Sir Lionel Whitby, on the challenge to medical education in the second half of the twentieth century, by Sir Richard Livingstone, on the definition of education, by Dr. John F. Fulton, on the history of medical education, and by S. M. K. Mallick, on the conception of medicine as a technology or as a profession. The papers read at the meeting are divided into four sections: requirements for entry into medical schools; aims and content of the medical curriculum; technics and methods of medical education; and preventive and social medicine. There are indexes of names and subjects, and the publishing is good. The volume is recommended for all medical libraries and all persons interested in education.

Die BCG-Schutzimpfung. Edited by Prof. Dr. med. Rolf Griesbach. 8°, cloth, 330 pp., with illustrations. Stuttgart: Georg Thieme, 1954. DM 16.50. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

In this new book on preventive inoculation with BCG *(Bacillus Calmette-Guérin)* the 6 authors discuss the subject in three parts: experimental studies and bacteriology, immunity and tuberculin allergy and action of the vaccination; methods and experience in Germany and Scandinavia; and critical analysis of the value of the process. The literature is reviewed, with lists of references appended to the chapters. There are indexes of authors and subjects. Interest in the method has been renewed recently; this book should be in all collections on the subject.

Current Concepts in Digitalis Therapy. By Bernard Lown, M.D.; and Samuel A. Levine, M.D., clinical professor of medicine, Harvard Medical School, and physician, Peter Bent Brigham Hospital. First edition. 12°, cloth, 164 pp., with 21 figures and 10 tables. Boston: Little, Brown and Company, 1954. $3.50.

The authors of this monograph present a comprehensive survey of the present knowledge of digitalis therapy. The literature is surveyed, and there is an extensive bibliography. The subject is discussed under a number of headings related to digitalis: action and clinical use, intoxication, electrolytes, relation of potassium to intoxication, paroxysmal tachycardia with block and a tolerance test. This important monograph should be in all collections on the heart.

Elements of Pediatric Anesthesia. By C. R. Stephen, B.Sc., M.D.C.M., F.A.C.A., D.A., (R.C.P. & S.) London, England, professor of anesthesiology, Duke University School of Medicine, and chief, Division of Anesthesia, Duke University Hospital, Durham, North Carolina. 8°, paper, 109 pp., with 25 illustrations. Springfield, Illinois: Charles C Thomas, 1954. $3.50. (Publication No. 232, *American Lecture Series.)*

This book covers thoroughly the problems of anesthesia in children, including the premature infant and the thymic child. It discusses premedication, basal anesthesia, technics, anesthetic drugs, surgical procedures, oxygen therapy and the treatment of asphyxia neonatorum. The pertinent literature is noted; there is a bibliography of 90 references, as well as a good index.

Group Therapy for Mothers of Disturbed Children. By Helen E. Durkin, Ph.D., supervising psychologist and lecturer for the Postgraduate Center for Psychotherapy and the Group Therapy Institute, New York City. 8°, cloth, 125 pp. Springfield, Illinois: Charles C Thomas, 1954. $3.50. (Publication No. 236, *American Lecture Series.*)

The author discusses the technic in the handling of mothers' groups and the various problems of group psychotherapy. There is a short bibliography and an index.

Ciba Foundation Symposium on Leukaemia Research. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Margaret Cameron, M.A., A.B.L.S.; assisted by Joan Etherington. 8°, cloth, 297 pp., with 56 illustrations. Boston: Little, Brown and Company, 1954. $6.75.

This symposium, held in London in November, 1953, was attended by 35 research workers from England, Europe and the United States. Twenty topics relating to leukemia were discussed. There is a good index. The book should be in all collections on the subject.

Cancer: Race and geography. Some Etiological, Environmental, Ethnological, Epidemiological, and Statistical Aspects in Caucasoids, Mongoloids, Negroids, and Mexicans. By Paul E. Steiner, Ph.D., M.D., professor of pathology, University of Chicago School of Medicine. 8°, cloth, 363 pp., with 73 illustrations and 50 tables. Baltimore: Williams and Wilkins, 1954. $5.00.

The author discusses cancer of the various organs of the body and reviews the literature. There are summaries of geographic and ethnic groups and a bibliography of 21 pages. The book should be in all collections on the subject.

Pulmonary Diseases. Edited by Roscoe L. Pullen, M.D., professor of medicine and dean, University of Missouri School of Medicine, and consultant to the Surgeon General, Department of the Army. 669 pp., with 195 illustrations, 4 plates (1 in color). Philadelphia: Lea and Febiger, 1955. $15.00.

This is a composite book written by 20 outstanding specialists. Lists of references are appended to the chapters. The publishing is excellent. This is the type of book that approximates a serial. It is recommended to all medical libraries and to all physicians interested in diseases of the respiratory system.

Fundamentals of Internal Medicine. By Wallace Mason Yater, M.D., M.S. (in med.), director, Yater Clinic, Washington, D. C. Fourth edition. 8°, cloth, 1276 pp., with illustrations. New York: Appleton-Century-Crofts, Incorporated, 1954. $13.50.

First published in 1938, this standard work has been revised and brought up to date. The author had the assistance of 21 contributors. Material has been added on the ganglion-blocking agents, anticholinergic drugs, ACTH and cortisone, newer diagnostic methods, recently described diseases such as herpangina, acute hemorrhagic fever, catscratch fever and others. Short lists of recommended references are appended to the chapters. There is a good index, and the publishing is excellent.

Stellate Ganglion Block: Techniques, indications, uses. By Daniel C. Moore, M.D., director, Department of Anesthesiology, Mason Clinic, and chief of anesthesia, Virginia Mason Hospital, Seattle, Washington. 4°, cloth, 280 pp., with 101 illustrations and 6 tables. Springfield, Illinois: Charles C Thomas, 1954. $12.50.

This is a comprehensive study of the stellate-ganglion block and its application to numerous medical and surgical conditions. The pertinent literature has been reviewed, and lists of references are appended to the chapters. The text is divided into three parts: general considerations; technics, signs and symptoms and complications; and clinical indications. There is an appendix on technics other than those of the author. There is a good index, and the publishing is excellent. The book comprises a standard reference work on the subject.

Clinical Measurement of Uterine Forces in Pregnancy and Labor. By S. R. M. Reynolds, Ph.D., D. Sc., staff member, Department of Embryology, Carnegie Institution of Washington, and lecturer in obstetrics, Johns Hopkins University School of Medicine; Jerome S. Harris, M.D., Department of Obstetrics and Gynecology, University of Colorado School of Medicine; and Irwin H. Kaiser, M.D., Ph.D., Department of Obstetrics and Gynecology, University of Minnesota Medical School. 8°, cloth, 328 pp., with 97 figures and 14 tables. Springfield, Illinois: Charles C Thomas, 1954. $9.50.

The authors review the literature on the subject. The text is divided into four parts: background and physiologic basis of tokodynamometer; methods; uterine contractions during pregnancy and labor; and effects of psyche and drugs on uterine contractions. There are indexes of authors and subjects. The monograph should be in all collections on obstetrics.

Antibiotics and Antibiotic Therapy: A clinical manual. By Allen E. Hussar, M.D., chief of Medical Service, Franklin Delano Roosevelt Veterans Administration Hospital, Montrose, New York; and Howard L. Holley, M.D., associate professor of medicine, Medical College of Alabama, and consultant in internal medicine, Veterans Administration Hospital, Tuscaloosa, Alabama. 8°, cloth, 475 pp., with 3 tables. New York: Macmillan Company, 1954. $6.00.

The authors have provided a useful book on the antibiotics and their therapeutic use. The text is divided into three parts as follows: fundamentals of antibiotic therapy; general description of the antibiotics in clinical use; and the drug of choice in different infections. This last section is comprehensive in scope, occupying almost two thirds of the text, and deals with bacterial, rickettsial, fungal and parasitic infections and diseases. There are also chapters on the specialized fields. Lists of references are appended to the material on the different antibiotics and infections, and the pertinent literature has been noted. There is a good index. The book should be in all collections on the subject.

D. M. Disease-a-month. No. 1. October, 1954. Annual subscription $9.00. Year Book Publishers, Chicago.

This new publication presents monthly clinical monographs on current medical problems. The first issue deals with rheumatic fever.

Doctors' Legacy: A selection of physicians' letters, 1721-1954. Edited by Laurence Farmer, M.D. With a foreword by Leona Baumgartner, M.D., Ph.D. 8°, cloth, 267 pp. New York: Harper and Brothers, 1955. $3.50.

This is an interesting series of letters dating from William Douglass (Boston, 1721) to Frederick C. Sharples (Greensboro, Vermont, 1953). The letters are from physicians of Great Britain and the United States. A number of Boston doctors are included: John Warren (1778), Benjamin Waterhouse (1794), John C. Warren (1799), James Jackson, James Jackson, Jr., John Ware, Henry I. Bowditch, Oliver Wendell Holmes and Harvey Cushing. A list of sources is appended to the text. The book is recommended for all history collections.

Perspectives and Horizons in Microbiology: A symposium edited by Selman A. Waksman. 8°, cloth, 220 pp., with illustrations. New Brunswick: Rutgers University Press, 1955. $3.50.

Sixteen persons took part in this symposium. The subjects are divided as follows: the microbe as a living part; metabolism of micro-organisms; and micro-organisms and higher forms of life. An appendix comprises the three addresses delivered at the dedication of the Institute of Microbiology of Rutgers University on June 7, 1954. Lists of references are appended to the articles.

Tumours of Lymphoid Tissue. By George Lumb, M.D., reader in pathology, Westminster Medical School, London University, consultant pathologist, Westminster Hospital, and lecturer in pathology, Institute of Basic Medical Science, Royal College of Surgeons of England. With a foreword by Sir Stanford Cade, K.B.E., C.B., D.Sc., F.R.C.S., M.R.C.P., F.F.R., senior surgeon, Westminster Hospital. 8°, cloth, 201 pp., with illustrations. Edinburgh: E. and S. Livingstone, Limited, 1954. (Distributed by Williams and Wilkins, Baltimore.)

Dr. Lumb discusses the terminology and classification, frequency and treatment of various types of tumors of the lymphoid tissue, benign and malignant. There is a bibliography of 230 references. The illustrative work and the publishing in general were done in Great Britain. The book is recommended for all collections on tumors.

Cardiac Anomalies: A clinicopathologic correlation. By Vincent Moragues, M.D., associate professor of pathology, Creighton University School of Medicine, and associate pathologist, Creighton Memorial, St. Joseph's Hospital, Omaha, Nebraska; and Chester P. Lynxwiler, M.D., assistant professor of pediatrics, St. Louis University School of Medicine, and director, Pediatric Heart Clinic, Firmin Desloge Hospital, St. Louis. 4°, cloth, 92 pp., with 157 illustrations. Baltimore: Williams and Wilkins, 1954. $6.50.

The authors of this atlas portray the congenital anomalies of the heart and great blood vessels. The conditions covered include malpositions, defects of the cardiac septums, valvular anomalies, anomalies of septation of the truncus arteriosus, transposition complexes, anomalies of the aortic arch and Ebstein's malformation of the tricuspid valve. The publishing is excellent. The atlas should be in all collections on cardiology.

Handbook of Radiology. Edited by Russell H. Morgan, M.D., professor of radiology, Johns Hopkins University School of Medicine, and radiologist-in-chief, Johns Hopkins Hospital; and Kenneth E. Corrigan, Ph.D., associate professor of radiology, Wayne University, and director, Radiological Research Department, Harper Hospital, Detroit. 12°, cloth, 518 pp., with tables and illustrations. Chicago: Year Book Publishers Incorporated, 1955. $10.00.

This handbook is the joint work of 15 specialists in their particular fields. The material is divided into six parts: definition of physical terms and units, including conversion formulas and tables; general physical and biophysical data; radiotherapeutics; radioactive isotopes; radiography and fluoroscopy; and radiation protection. The part on radiographic technic is well illustrated, with 53 drawings of projections. The book should prove useful as a reference source.

Diagnostic Laboratory Hematology. By George E. Cartwright, M.D., associate professor of medicine, University of Utah College of Medicine. 8°, cloth, 104 pp., with 28 tables. New York: Grune and Stratton, 1954. $3.00.

This manual presents in concise form the essential details of procedures commonly used in student laboratories and doctors' offices. The author has selected a single method for each determination on the basis of his experience. There is an index; the publishing is excellent.

Urology. Vol. 1, 2 and 3. Edited by Meredith Campbell, M.S., M.D. 8°, cloth, 2356 pp., with 1148 figures. Philadelphia: W. B. Saunders Company, 1954. $60.00.

This new system of urology is a much needed set on its subject. The text is the work of 51 specialists, and the coverage is extensive. The first volume deals with anatomy and physiology, diagnosis, pathology of urinary obstruction, embryology and anomalies of the urogenital tract, infections and inflammations of the urinary tract and male genital tract, infertility in the male and urinary lithiasis and foreign bodies. The second volume considers injuries, tumors and neuromuscular disease of the urinary tract, and urology in the female and in infancy and childhood. The third volume discusses endocrinology in urology, urologic surgery, radiation treatment of tumors of the genitourinary organs, and medical diseases of the kidneys and the adrenal glands. Lists of references are appended, and there is an index to the complete text in each volume. The publishing is excellent. The set is recommended as a standard work for all medical libraries.

Pharmacology in Medicine: A collaborative textbook. Edited by Victor A. Drill, Ph.D., M.D., lecturer in pharmacology, Northwestern University Medical School. 4°, cloth, various pages with illustrations. New York: McGraw-Hill Book Company, Incorporated, 1954. $19.50.

This comprehensive textbook is the joint work of 80 contributors. The authorship of the articles is indicated, making the book a semiserial. The text is divided into 18 parts. The first deals with history, general principles and prescription writing, the second to fifth with anesthetics, general and local, adjuncts and sedation, hypnosis and analgesia, the sixth and seventh with central-nervous-system stimulants and the autonomic nervous system, the eighth with the cardiovascular system, the ninth with water and salt balance, the tenth with allergy, the eleventh with the gastrointestinal tract, the twelfth with dermatomucosal agents, the thirteenth with the hematopoietic system, the fourteenth with metals and radioactive elements, the fifteenth with gases, vapors and dusts, the sixteenth with vitamins and other nutritional factors, the seventeenth with the endocrine glands and accessory reproductive organs, and the eighteenth with specific chemotherapy. Lists of references are appended to the subjects, and there is a good index. The price is not excessive for the size of the volume. This valuable book is recommended for all medical libraries.

Transactions of the American College of Cardiology. Vol. 3, 1953. Edited by Bruno Kisch, M.D., Robert P. Glover, M.D., and Ashton Graybiel, M.D. 8°, paper, 259 pp., with illustrations. New York: American College of Cardiology, 1954.

NOTICES

ANNOUNCEMENTS

Dr. Arthur I. Tartakoff announces the opening of his office for the practice of obstetrics and gynecology at 483 Beacon Street, Boston, Massachusetts.

Dr. Augustus Thorndike announces the closing of his office at 319 Longwood Avenue, Boston, as of July 1, 1955, to accept a full-time appointment as chief surgeon to the Department of Hygiene at Harvard University.

Dr. Setrag A. Zacarian announces the opening of an office for the practice of dermatology at the Medical Center Building, 130 Maple Street, Springfield, Massachusetts.

INSTITUTE OF PSYCHIATRIC TREATMENT

The Institute of Psychiatric Treatment will be conducted under the direction of Drs. Leo Alexander and Robert Arnot, Reception Building, Boston State Hospital, September 29 through October 1. Further details may be obtained from Dr. Leo Alexander, 433 Marlborough Street, Boston 15.

SOCIETY MEETINGS AND CONFERENCES

August and September. Beth Israel Hospital Course. Page 509, issue of March 24.

August 22 and August 23. Consultation Clinics for Crippled Children in Massachusetts. Page 1099, issue of June 23.

August 28–September 2. American Congress of Physical Medicine and Rehabilitation. Page 157, issue of January 27.

August 30 and 31 and September 1. New England Health Institute. Page 1010, issue of June 9.

September 12–21, December 5–14, 1955, January 30–February 8, March 19–28 and June 4–13, 1956. Army Medical Service Postgraduate Course. Page 84, issue of July 14.

September 14–17. Heart-Disease Seminar. Page 260, issue of August 11.

September 21. Essex North District Medical Society. Page 208, issue of August4.

September 21. New Jersey Neuro-Psychiatric Institute. Page 208, issue of August 4.

September 29–October 1. Institute of Psychiatric Treatment. Notice above.

September 30–October 1. American Medical Writers' Association. Page 118, issue of July 21.

October 1 and 2 and 3–6. American Academy of Pediatrics. Page 118, issue of July 21.

October 5. Arthritis and Rheumatism Foundation. Page 208, issue of August 4.

October 6–8. Academy of Psychosomatic Medicine. Page 509, issue of March 24.

October 10–21. New York Academy of Medicine. Graduate Fortnight. Page 84, issue of July 14.

October 19 and December 14, 1955 and February 15, March 28 and April 18, 1956. Greater Boston Medical Society. Page 208, issue of August 4.

October 22–26. American Heart Association. Scientific Session. Page 603, issue of April 7.

October 23–27. American Institute of Dental Medicine. Page 414, issue of March 10.

October 26 and November 30, 1955 and January 25, March 21 and April 26, 1956. Phi Delta Epsilon Fraternity Graduate Club Program. Page 118, issue of July 21.

October 27–29. Congress of Neurological Surgeons. Page 208, issue of August 4.

November 1–3. Henry Ford Hospital Symposium on Enzymes. Page 920, issue of May 26.

November 6–13. Second International Congress of Allergology. Page 157, issue of January 27.

November 7–9. Association of Military Surgeons of the United States. Page 118, issue of July 21.

November 11 and 12. Inter-Society Cytology Council. Page 1056, issue of June 16.

November 14 and 25. Course in Laboratory Diagnosis of Tuberculosis. Page 1102, issue of June 23.

November 19–21. American Association of Blood Banks. 8th Annual Meeting. Palmer House, Chicago, Illinois.

November 28–December 2. Interim Session of the American Medical Association, Boston.

March 24 and 25, 1956. American Psychosomatic Society. Page 260, issue of August 11.

Calendar for the Week Beginning Thursday, August 25

Thursday, August 25

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.

*11:00 a.m.–12:00 m. Thoracic Conference. Pulmonary Neoplasms. Dr. Harrison Black. Main Amphitheater, Peter Bent Brigham Hospital.

*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.

*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

*12:15–1:15 p.m. Orthopedic Clinic. Amphitheater, Peter Bent Brigham Hospital.

(Concluded on page xxi)

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REFERENCE: 1. Kirwin, T. J., Lowsley, O. S., and Menning, J., *Am. J. Surg.* **62**:330-335, December 1943.

(Concluded from page 302)

FRIDAY, AUGUST 26
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.

SATURDAY, AUGUST 27
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–10:00 a.m. Surgical Grand Rounds. Drs. Charles G. Child, III, A. J. A. Campbell and staff, First (Tufts) Surgical Service, New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

MONDAY, AUGUST 29
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Surgical Conference Room, Peter Bent Brigham Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.
5:15 p.m. Staff Meeting. Harris Hall, New England Deaconess Hospital.

TUESDAY, AUGUST 30
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Joslin Clinic. (Cafeteria) New England Deaconess Hospital.
*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.

WEDNESDAY, AUGUST 31
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Boston State Hospital Psychiatry Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*7:30–9:30 p.m. Lahey Clinic Lecture. Joslin Auditorium, New England Deaconess Hospital.

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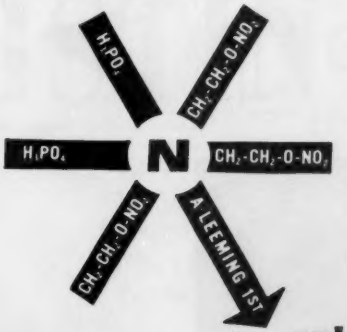

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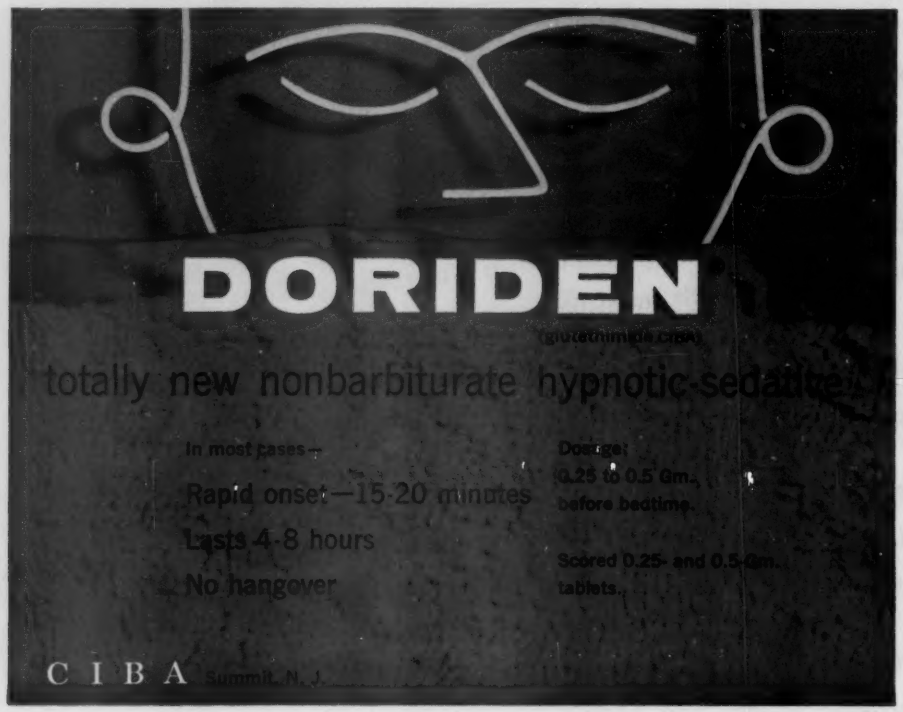

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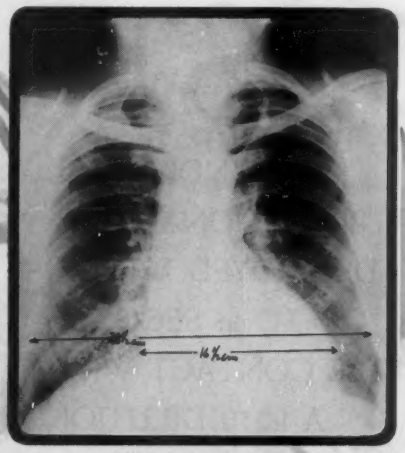

(X-ray, enlarged heart)

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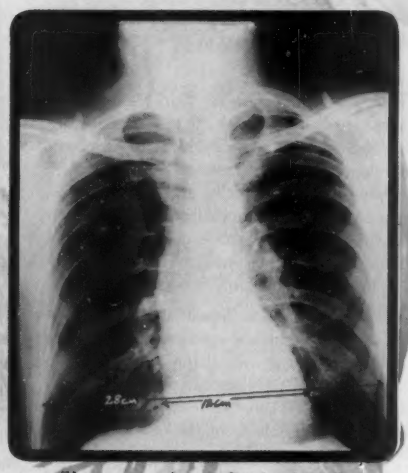

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1. Davis, C. H.: J.A.M.A. 157:126 (Jan. 8) 1955. 2. Davis, C. H.: Am. J. Obst. & Gynec. 68:559 (Aug.) 1954. 3. Davis, C. H.: West. J. Surg. 63:53 (Feb.) 1955. 4. Davis, C. H.: J.A.M.A. 92:806 (Jan. 26) 1929.

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2. Sebrell, W. H., Jr.: J.A.M.A., 152:42 (May) 1953.
3. Sherman, R. J., M.D.: Medical Times, 82:107 (Feb.) 1954

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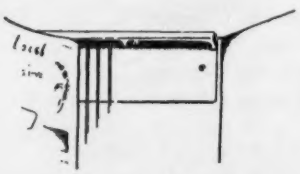

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Index to Advertisers

PAGE

Abbott Laboratories ..... viii, ix
The Armour Laboratories xxxiii
Baldpate, Inc. xxxi
Boston Medical Laboratory xxix
Ciba Pharmaceutical Products, Inc. ..... vii, xxiv, Back Cover
Coca-Cola Company xxiv
David Memorial Nursing Home xxxi
Electroencephalographic Laboratory, Inc. xxix
Endo Products, Inc. xi
Fine Chemicals xxx
Glenside, Inc. xxxi
Hanover House, Inc. xxxi
Hoffmann-La Roche, Inc. ..... After xiv
Institute of Psychiatry vi
Irwin, Neisler & Company xxv
Lederle Laboratories ..... xvi, xvii
Thos. Leeming & Co., Inc. xxi
Eli Lilly and Company xviii
The S. E. Massengill Company xxviii
McNeil Laboratories, Inc. ..... xxii, xxiii
Medical Clearing Bureau, Inc. xxxii
Parke, Davis and Company ..... ii, iii
Perkins School xxxi
Pfizer Laboratories (Div. of Chas. Pfizer & Co., Inc.) xxvii
Plymouth Rock Gelatine Co. xxxii
Ring Sanatorium xxxi
W. B. Saunders Company ..... Front Cover
Julius Schmid, Inc. xxvi
G. D. Searle and Company xix
Sharp & Dohme (Division of Merck & Co., Inc.) ..... iv, xx
Smith, Kline & French Laboratories v
E. R. Squibb & Sons (Division of Mathieson Chemical Corporation) xv
Storrow House (Massachusetts General Hospital) xxxi
United States Brewers Foundation xii
The Upjohn Co. xiii
Warner-Chilcott Laboratories x
Washingtonian Hospital xxxii
J. S. Waterman & Sons xxxi
White Laboratories, Inc. xiv
Wiswall Sanatorium xxxi
Woodside Cottages, Inc. xxxi

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